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ANNALS OF
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SPECIFIC TREATMENT OF THE PNEUMOCOCCIC PNEUMONIAS; AN ANALYSIS OF THE RESULTS OF SERUM THERAPY AND CHEMOTHERAPY AT THE BOSTON CITY HOSPITAL FROM JULY 1938 THROUGH JUNE 1939 *

By MAXWELL FINLAND, F.A.C.P., WILLIAM C. SPRING, JR., and FRANCIS C. LOWELL, *Boston, Massachusetts*

DURING the past few months, in accord with the general trend in the treatment of bacterial infections, the focus of attention in the literature dealing with the therapy of pneumonia has shifted from specific serums to chemotherapy. This was quite natural and is easy to appreciate in a disease like pneumonia, where specific serotherapy is rather laborious, expensive and subject to a number of important limitations, in contrast to chemotherapy, which is simple to administer, relatively inexpensive and has a wider scope of usefulness. The generally favorable results more or less universally obtained with sulfapyridine have fully justified this shift in emphasis. Nevertheless, the fact that specific antipneumococcic serums, within their limitations, are highly effective in radically reducing the death rate and curtailing the acute disease in cases of pneumococcic pneumonia is now attested by a wide experience perhaps as thoroughly controlled as any therapy can be in such a disease. Furthermore, recent results with serotherapy have shown steady improvement with its extension to include more types of pneumococci, and particularly with the introduction of rabbit serums which have proved highly effective against infections with the common pneumococcus types other than Type III.[1] Adequate data are not yet available for the proper evaluation of the relative merits of the newer chemotherapeutic agents and the recent serums, nor is it possible as yet to delineate the scope of usefulness of these agents when given separately or in combination.

In this paper we wish to present an analysis of the results of serotherapy

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

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and chemotherapy in pneumococcic pneumonia in adults as carried out at the Boston City Hospital during the 1938 to 1939 season. This experience is of especial interest since (1) serums and chemicals were used separately and in combination; (2) all of the cases admitted to the hospital that received neither of these forms of therapy are also included; and (3) similar data accumulated under more or less comparable conditions over a number of years in the same hospital are available for comparison.[2] Although the number of cases included may appear at first glance to be large, so many factors require close scrutiny that only the more important ones involved in the proper evaluation of the present therapy can receive adequate attention.

Patients, Materials and Methods

The patients included in this study were admitted to the Boston City Hospital between July 1, 1938 and June 30, 1939. They were all over 12 years of age, each had an acute respiratory infection with consolidation in the lung, demonstrated in almost every instance either by roentgenogram or at necropsy, and pneumococci were identified and typed on one or more occasions from sputum and/or other sources such as blood, lung or purulent exudates.

The diagnostic typing serums, most of the therapeutic serums and the bulk of the sulfapyridine were supplied through the generosity of the Lederle Laboratories, Inc. Therapeutic horse serums were also furnished by the Antitoxin and Vaccine Laboratory of the Massachusetts Department of Public Health, some of the therapeutic rabbit serums by the Squibb Laboratories and part of the sulfapyridine supply by Merck and Company and Calco Chemical Company. Sulfapyridine became available to us during the latter part of October, and the supply of this drug was limited at first. All of the lots of therapeutic serums were refined and concentrated, and, for the most part, were supplied for clinical trial prior to their release for general use.

No attempt was made to carry out a controlled therapeutic experiment, since previous experience has convinced us that in such a highly fatal disease strict alternation of any sort is impractical and, indeed, grossly misleading when agents with known lifesaving properties are available. In general, sulfapyridine was first used alone in relatively mild cases, when multiple "higher" types were found, in cases in which potent serums were not available or where no striking benefits were to be expected from them. Treatment with this drug was begun simultaneously with specific serum therapy in cases with the poorest prognoses, and the two agents were used in sequence when the response to one or the other seemed inadequate or when severe untoward symptoms were encountered from one of them. The use of the drug was gradually extended, so that in the latter part of the season most patients who were acutely ill were given sulfapyridine as soon as the clinical diagnosis was made, but only after sputum was obtained for typing and blood for culture. Serum was then given to some of the severest cases

as soon as the type was obtained, and to others as soon as it was felt that response to the drug was not satisfactory or when severe untoward reactions were encountered. Sulfanilamide was used in a number of cases, particularly in the first half of the season, in more or less the same manner as during the previous year.[2]

A large number of cases are included that received neither serum nor sulfapyridine.* For the most part these included: patients whose illness appeared mild and who recovered spontaneously; those who, when the bacteriological diagnosis was made, had already died or had shown sufficient improvement so that no specific therapy was required; a number in whom the pneumonia complicated other diseases which obscured the signs and symptoms; and, finally, some cases with atypical signs, symptoms and course. Actually the choice of cases for therapy is much better judged in retrospect and will be brought out in the analysis which follows.

Analysis of the Cases and of the Results of Therapy

Proper appreciation of the full value and limitations of any therapeutic agent in the treatment of pneumonia requires a careful analysis of the important factors in the host and in the infection which influence the prognosis, as well as the factors concerning the remedy used and its untoward effects. These will be considered in as much detail as the volume of data seems to warrant. As far as possible, the data will be presented in tabular form so as to permit comparisons of the various forms of therapy. For the sake of brevity, these data will only be summarized in the text and such facts will be brought out as are not directly apparent from the tables. Sulfanilamide was used in the treatment of a number of the cases which are included among those who received serum and among those who received neither serum nor sulfapyridine. To avoid confusion, the effects of sulfanilamide will not be noted in all the tables, but will be considered in a separate section.

Table I

Gross Mortality Rates—Pneumococcic Pneumonia—Boston City Hospital, 1938–1939

Therapy	No. of Cases	Died	Per cent Died
Specific serum	211	28	13.3
Serum and sulfapyridine	129	31	24.0
Sulfapyridine	225	40	17.8
No serum, no sulfapyridine *	472	135	28.6
Total	1037	234	22.6

* Includes 73 cases in which the bacteriological diagnosis was made after death. If these are excluded, there were 399 cases with 62 deaths, or 15.5 per cent.

Gross Fatality. These figures are shown in table 1. Several significant points may be mentioned, since they will not appear in the tables.

* These cases will be referred to as "untreated" and all the others will be referred to as specifically treated. Those who received sulfanilamide alone are included among the "untreated" cases.

"Specific treatment," which for the pneumococcic pneumonias can now be considered to include serum or sulfapyridine or both, was used during this year in 565, or 54 per cent of the 1037 cases. Among these 565 treated cases there were 99 deaths, or 17.5 per cent. In the seven years prior to July 1936, there were 2648 cases of pneumococcic pneumonia, of which 470, or 16.5 per cent, were treated with specific serums; among the latter, 19 per cent died. In these seven years, 43 per cent of all the cases died, as compared with 22.6 per cent during 1938 to 1939. In other words, although the reduction in death rate among specifically treated cases was slight (from 19 to 17.5 per cent), the total death rate among all the adult cases of pneumococcic pneumonia was reduced to about one-half, due largely to the extension of treatment to a considerably greater proportion of the severe cases. In the two intervening years, as already pointed out,[2] serum treatment was being extended by the inclusion of cases treated late in the disease and also cases due to additional pneumococcus types for which serums became available. The greatest extension of treatment, however, occurred in the 1938 to 1939 season with the introduction of sulfapyridine and the increased availability of rabbit serums. That the residue of cases treated without serum or drugs during 1938 to 1939 includes a greater proportion of milder cases than in previous years is indicated by the death rate of 28.6 per cent in this group, as compared with 45 per cent in the non-serum treated cases prior to July 1936, and about 40 per cent in similar cases due to the common types of pneumococci during the following two years.[2] The incidence of bacteremia was also considerably lower in the untreated cases during 1938 to 1939.

Monthly Variations. The death rates shown in table 1 are essentially the same as those given in our preliminary report, which included the cases treated prior to March 15 of the same season.[3] The present report includes more than twice as many recipients of sulfapyridine. The numbers of cases treated each month are shown in table 2. Only a small proportion of cases received sulfapyridine during October and November, about one-third of all the cases received the drug during the following two months and about one-half of all the patients were given the chemical during February and thereafter. There were wide fluctuations in proportion of deaths from month to month, the variations being greatly exaggerated because of the relatively small numbers involved. There was no obvious correlation, however, between the proportion of cases receiving the different kinds of therapy and the death rates in each group.

Types of Pneumococci (Table 3). Here we begin to observe the first important differences in the selection of cases for the various forms of therapy. Types I, II, IV, V, VII and VIII which, excluding Type III, are the six most frequent types in the pneumonia of adults, are also the types which are most regularly associated with typical and primary lobar pneumonia.[2a] These six types represented 84, 78, 51 and 23 per cent, respectively, of the cases treated with serum alone, serum and sulfapyridine,

sulfapyridine and neither agent. Among the cases of these types, the mortality rates for the four groups, in the same order, were 12, 22, 13 and 31 per cent.

TABLE II

Distribution of Cases According to the Month During Which the Patients Were Admitted to the Hospital

Month	Specific Serum		Serum and Sulfapyridine		Sulfapyridine		No Serum, No Sulfapyridine		All Cases	
	Number	Died	Number	Died	Number	Died	Number	Died	Number	Died
1938										
July	7^{3}	0	0	—	0	—	17^{1}	6^{1}	24^{4}	6^{1}
August	11^{4}	4^{3}	0	—	0	—	33^{2}	14^{2}	44^{6}	18^{5}
September	14^{5}	4^{4}	0	—	0	—	23	10	37^{5}	14^{4}
October	29^{6}	3^{2}	2^{1}	1^{1}	1	1	41^{7}	8^{6}	73^{14}	13^{8}
November	21^{4}	4^{1}	7^{3}	3^{3}	3	0	38	9	69^{7}	16^{4}
December	24^{5}	0	23^{11}	4^{4}	8^{1}	2	55^{2}	14^{2}	110^{19}	20^{6}
1939										
January	38^{14}	5^{5}	28^{16}	9^{6}	20^{3}	7^{3}	54^{4}	17^{4}	140^{37}	38^{18}
February	10^{3}	1^{1}	16^{7}	2^{2}	45^{10}	8^{3}	67^{3}	12^{2}	138^{23}	23^{8}
March	15^{7}	3^{2}	20^{13}	6^{6}	53^{15}	5^{3}	57^{5}	18^{5}	145^{40}	32^{16}
April	21^{5}	3^{2}	23^{17}	4^{4}	36^{8}	6^{4}	45^{3}	12^{3}	125^{33}	25^{13}
May	18^{2}	0	8^{4}	1^{1}	43^{11}	7^{4}	24^{1}	6^{1}	93^{18}	14^{6}
June	3^{1}	1^{1}	2^{2}	1^{1}	16^{3}	4^{2}	18^{2}	9^{2}	39^{8}	15^{6}
Totals	211^{69}	28^{21}	129^{74}	31^{28}	225^{61}	40^{19}	472^{30}	135^{27}	1037^{214}	234^{95}

Superscripts represent numbers of patients with pneumococcus bacteremia.
The patients in whom the onset of the disease occurred in the hospital are listed according to the time of onset.

The Type III cases are of especial interest. Eighty cases due to this type were treated with serum or sulfapyridine, or both, with 15 deaths (19 per cent), as compared with 21 deaths, or 33 per cent, of the 63 who received no specific treatment. Prior to July 1936, the mortality in this type over a seven-year period was 60 per cent, and during the next two years it was 47 per cent in untreated cases and 43 per cent among 67 cases treated with serum or sulfanilamide, or both.[26] However, bacteremia was less frequent in the present cases; only 15 of the treated cases (19 per cent) and 5 of those not treated specifically (8 per cent) had positive cultures, as compared with a 36 per cent bacteremic incidence prior to 1936 and 26 per cent in the two intervening years. It is significant, nevertheless, that six bacteremic Type III cases recovered following treatment during this year. All of these six cases received sulfapyridine and only one received serum in addition.

Among the so-called "higher" types, comparisons are difficult since serums were used only in the severest cases. This is indicated by the high incidence of bacteremia in those receiving serum, particularly where it was used to supplement sulfapyridine therapy.

TABLE III

Distribution of Cases and Deaths According to Pneumococcus Types

Type	Specific Serum		Serum and Sulfapyridine		Sulfapyridine		No Serum, No Sulfapyridine		All Cases	
	No.	Died	No.	Died	No.	Died	No.	Died *	No.	Died
I	69^{14}	5^{4}	54^{38}	14^{13}	58^{25}	8^{7}	16^{2}	4^{2} (4)	197^{79}	31^{26}
II	29^{11}	7^{4}	22^{12}	4^{4}	8^{3}	2^{2}	10^{3}	2^{2} (1)	69^{29}	15^{12}
III	11^{3}	3^{3}	19^{3}	3^{2}	50^{9}	9^{4}	63^{5}	21^{5} (9)	143^{20}	36^{14}
IV	11^{2}†	0	3^{2}	1^{1}	7^{3}	2^{2}	16^{2}	6^{2} (3)	37^{9}	9^{5}
V	20^{7}	5^{5}	9^{5}	0	12^{2}	1^{1}	11^{3}	7^{3} (4)	52^{17}	13^{9}
VI	4	0	—	—	5	1	28^{1}	7^{1} (5)	37^{1}	8^{1}
VII	24^{6}	3^{2}	7^{4}	1^{1}	15^{1}	0	20^{1}	2 (2)	66^{11}	6^{3}
VIII	24^{7}	1^{1}	6^{2}	2^{1}	14^{1}	2	35^{2}	12^{2} (4)	79^{12}	17^{4}
IX	2^{1}	0	—	—	7	0	32^{2}	9^{2} (3)	41^{3}	9^{2}
X	1^{1}	0	—	—	1	0	20^{1}	4^{1} (2)	22^{2}	4^{1}
XI	1	1	—	—	5	2	17^{1}	3^{1}	23^{1}	6^{1}
XII	2^{1}	0	—	—	2^{1}	1^{1}	11^{1}	2	15^{3}	3^{1}
XIII	—	—	—	—	1	0	15	1 (1)	16	1
XIV	3^{2}	0	2^{1}	1^{1}	8^{3}	3^{2}	8^{1}	3^{1} (1)	21^{7}	7^{4}
XV	1^{1}	1^{1}	—	—	2	1	8	1 (1)	11^{1}	3^{1}
XVI	—	—	1^{1}	1^{1}	2	0	8	0	11^{1}	1^{1}
XVII	—	—	1^{1}	0	3	1	18^{1}	10^{1} (5)	22^{2}	11^{1}
XVIII	4^{1}	1	—	—	8^{1}	3	20^{2}	3^{2} (2)	32^{4}	7^{2}
XIX	2^{2}	0	2^{2}	1^{1}	5	1	23^{1}	8^{1} (6)	32^{5}	10^{2}
XX	—	—	1^{1}‡	1^{1}	2^{1}	0	16	8 (6)	19^{2}	9^{1}
XXI	—	—	—	—	1^{1}	0	7	2 (2)	8^{1}	2
XXII	1	0	—	—	3	2	11	1	15	3
XXIII	—	—	1^{1}	1^{1}	2	1	11	5 (4)	14^{1}	7^{1}
XXIV	—	—	—	—	—	—	7	3 (1)	7	3
XXV	1^{1}	1^{1}	1^{1}	1^{1}	—	—	4	1 (1)	6^{2}	3^{2}
XXVII	1	0	—	—	—	—	3	1	4	1
XXVIII	—	—	—	—	—	—	5	2 (2)	5	2
XXIX	—	—	—	—	2	0	20^{1}	6^{1} (3)	22^{1}	6^{1}
XXXI	—	—	—	—	2	0	4	1 (1)	6	1
Not I–XXXII	—	—	—	—	—	—	5§	0	5	0
Total	211^{59}	28^{21}	129^{74}	31^{28}	225^{51}	40^{19}	472^{30}	$135^{27}(73)$	1037^{214}	234^{95}

Superscripts represent numbers of patients with pneumococcic bacteremia.

* Parentheses enclose numbers of cases in which the bacteriological diagnosis was made after death.

† One case had Type XX in addition and received serum for both types.

‡ Types VI and XX in blood cultures in this case.

§ 4 of these cases had a pneumococcus that reacted with Types XI and XVI serums.[8]

Incidence of Bacteremia and Effect on Mortality (Table 4). Bacteremia was demonstrated before treatment in 184, or 32.6 per cent of the 565 specifically treated cases. This was about four and one-half times as frequent as among the untreated cases. Among the patients treated with both serum and sulfapyridine it was more than twice as frequent as among those treated with either agent alone. This would indicate that, from the point of view of the pneumococcic infection in the lung, a severer and more typical group of cases was chosen for specific treatment, and the worst of these received both serum and drug. As in all our previous reports, the

TABLE IV

Mortality in Relation to Results of Blood Cultures
Pneumococcic Pneumonia—Boston City Hospital 1938–1939

Therapy	Cases with Positive Blood Cultures			Per cent Positive	Cases with Negative Blood Cultures		
	No. of Cases	Died	Per cent Died		No. of Cases	Died	Per cent Died
Specific serum	59	21	35.6	28.0	152	7	4.6
Serum and sulfapyridine	74	28	37.8	57.4	55	3	5.5
Sulfapyridine	51	19	37.2	22.7	174	21	12.1
No serum, no sulfapyridine *	30	27	90.0	7.3	380	96	25.3
Total	214	95	44.4	21.9	761	127	16.7

* In 16 of the bacteremic cases and in 53 of the non-bacteremic cases, the bacteriological diagnosis was made after death. No blood cultures were made in 62 cases of this group, of whom 12 died (19.4 per cent).

TABLE V

Qualitative Variations in the Results of Blood Cultures in Relation to Specific Serum and/or Sulfapyridine Therapy 1938–39

	Serum		Serum and Sulfapyridine		Sulfapyridine		Serum and/or Sulfapyridine	
	No.	Died	No.	Died	No.	Died	No.	Died
Results of multiple cultures made before treatment								
First positive, then negative	4	0	7	1	8	1	19	2
First negative, then positive	11	4	12	2	4	0	27	6
All positive	20	8	35	15	16	8	71	31
Blood cultures negative before treatment and positive after treatment	1	1	2	2	6	2	9	5
Blood cultures positive before treatment								
Positive after treatment	8	6	20	9	12	7	40	22
Negative after, then positive again	2	2	3	3	1	0	6	5
Negative after treatment (fatal)	—	8	—	16	—	9	—	33

Only blood cultures yielding growth of pneumococci are listed here as positive.

Hemolytic streptococci were obtained in blood cultures taken after therapy from 10 patients, as follows:

Serum treated—4 bacteremic (pneumococcus) cases and 1 non-bacteremic case; one of the former recovered, all the others died.

Serum and sulfapyridine—4 bacteremic patients, of whom 2 died.

Sulfapyridine—1 non-bacteremic patient, who recovered.

mortality among bacteremic cases was three or more times as great as in non-bacteremic cases, regardless of the kind of treatment used.

The variations that were noted in the results of blood cultures taken during the acute disease in relation to therapy are summarized in table 5. There were 19 patients in whom the blood culture taken just before treatment was begun was sterile, although previous cultures were positive for pneumococci. Only two of these patients died. In a somewhat larger number of cases the reverse was true—the culture taken just prior to treatment was positive, whereas previous cultures were negative. There were six deaths among 27 such patients. All the six fatal cases received serum and two of them also received sulfapyridine. The mortality was considerably higher when multiple cultures taken before treatment were all positive, and this was true regardless of the therapy given.

Of especial interest are the nine patients in whom the first positive blood culture was obtained after treatment was begun, although cultures taken before treatment were all sterile. The one case that received serum alone had Type III pneumococcic pneumonia and delirium tremens. Cultures of blood taken on two occasions before treatment was begun were sterile, but a third one obtained 12 hours after 80,000 units of Type III serum had been given yielded 550 colonies per cubic centimeter of blood. In the meantime the patient had developed increasing "collapse," although there were no obvious reactions in relation to therapy. One of the patients who received serum followed by sulfapyridine had persistently positive cultures for Type I pneumococcus after treatment. He had thrombophlebitis, pyarthrosis and probably endocarditis. In the seven remaining patients the first positive blood culture was obtained from 8 to 20 hours after sulfapyridine therapy was started. The one patient among them who received serum in addition subsequently had sterile cultures, but he succumbed to a cranial lesion which preceded the onset of his pneumonia.

The mortality was particularly high among those bacteremic patients in whom the blood stream was not rapidly sterilized following therapy, that is, if any of the blood cultures taken after the beginning of treatment were still positive. This was true regardless of whether serum or drug, or both, were used. The five serum recipients, including three who received sulfapyridine in addition, whose blood streams were only temporarily sterilized following treatment, all had bacterial endocarditis. In a considerable number of bacteremic patients, death occurred in spite of repeatedly negative blood cultures following therapy, even including the heart's blood in those who came to autopsy. Many of them died with purulent focal complications. It is of interest that 8 of the 10 treated patients who had superinfections with hemolytic streptococci had pneumococcus bacteremia before treatment.

One patient treated late in the disease had a positive blood culture for Type XX pneumococcus before therapy. Following the administration of Type XX antipneumococcus rabbit serum and sulfapyridine, sterile blood

cultures were obtained. Cultures taken on the fourth day after sulfapyridine was discontinued and later were again positive, and these all showed both Type XX and Type VI pneumococci. Both these types were also obtained from cultures of endocardial vegetations found at autopsy.

Quantitative blood cultures in agar pour plates were made in about one-half of the bacteremic cases. The results are summarized in table 6. As

TABLE VI

Summary of Results of Quantitative Blood Cultures in Bacteremic Cases

Number of Colonies per c.c. of Blood	Serum Treated		Serum and Sulfapyridine		Sulfapyridine		All Treated Cases	
	Number	Died	Number	Died	Number	Died	Number	Died
0*	4	0	6	1	4	0	14	1
1–25	12	7	18	3	7	2	37	12
26–100	5	3	7	1	5	3	17	7
100+	3	3	13	10	8	8	24	21
Total	24	13	44	15	24	13	92	41

* Broth cultures positive, no growth in agar pour plate with 1 and 2 c.c. of blood.

was to be expected, the mortality was greatest among those patients whose blood yielded a growth of large numbers of pneumococci. The only three patients who recovered during this year when more than 100 colonies per cubic centimeter of blood were found before treatment all received both serum and sulfapyridine. Their cultures yielded 550, 400 and 149 colonies, respectively. The one with the 550 colonies was a woman of 69 who recovered without complications of the pneumonia, although she sustained a Colles's fracture and facial injury after falling out of bed while still under treatment. The other two patients both developed empyema; the one with 400 colonies recovered following repeated thoracenteses without operation and the other recovered following closed thoracotomy.

Effect of Age. From table 7 it is apparent that most of the older patients were treated with sulfapyridine by choice. This was due, in part, to the greater proportion of cases due to Type III and to the "higher" types, and in part to the fact that very favorable results had not been obtained in the older age groups in previous years. The severest among these patients received serum, in addition. Considering that two-thirds of the patients over 60 years of age who were treated with both serum and sulfapyridine had positive blood cultures, the death rate of less than 30 per cent in 37 such cases is remarkable. Only about one-fourth of the 62 patients over 60 years old and treated with sulfapyridine alone had positive blood cultures, and the mortality was 30 per cent. This is far better than previous death rates in this age group obtained with other kinds of therapy, including specific serums. The number of patients over 60 who were treated with

TABLE VII

Mortality in Relation to Age

Age Group (years)	Therapy														
	Specific Serum			Serum and Sulfapyridine			Sulfapyridine			No Serum, No Sulfapyridine			All Cases		
	No.	Died	%	No.	Died	%	No.	Died	%	No.	Died	%	No.	Died	%
13–19*	31^{6}	1^{1}	3	5^{5}	3^{3}	60	23^{2}	1	4	42	1	2	101^{13}	6^{4}	5.9
20–29	41^{10}	1^{1}	2	12^{3}	0	0	24^{4}	4^{1}	17	75^{2}	5^{1}	7	152^{19}	10^{3}	6.6
30–39	57^{14}	6^{3}	11	25^{15}	6^{6}	24	32^{8}	5^{1}	16	60^{3}	9^{3}	15	174^{40}	26^{13}	14.9
40–49	36^{12}	7^{6}	19	25^{16}	7^{7}	28	47^{15}	6^{4}	13	87^{4}	12^{3}	14	195^{47}	32^{20}	16.9
50–59	31^{10}	6^{5}	19	25^{11}	5^{3}	20	37^{7}	6^{3}	16	66^{5}	24^{4}	36	159^{33}	41^{15}	27.2
60–69	12^{6}	6^{4}	50	26^{16}	6^{5}	23	36^{8}	8^{5}	22	70^{8}	35^{8}	50	144^{38}	55^{22}	38.2
70+	3^{1}	1^{1}	33	11^{8}	4^{4}	36	26^{7}	10^{6}	38	72^{8}	49^{8}	68	112^{24}	64^{18}	57.1
Total	211^{59}	28^{21}	13	129^{74}	31^{28}	24	225^{51}	40^{19}	18	472^{30}	135^{27}	29	1037^{214}	234^{95}	22.6

* Superscripts represent numbers of bacteremic cases.

serum alone is too small for comparison. These represented more typical cases than those receiving sulfapyridine alone; almost all were due to the common types. The incidence of bacteremia among them was higher, as was also the death rate. Obviously the best results in the older age groups were obtained with the combination of serum and sulfapyridine. Among the younger patients, the apparently higher death rates with the combination therapy were obviously due to the inclusion in this group of the severest

TABLE VIII

Mortality in Relation to the Duration of the Disease When Treatment Was Begun

Day Treatment Begun *	Therapy														
	Specific Serum			Serum and Sulfapyridine			Sulfapyridine			No Serum, No Sulfapyridine			All Cases		
	No.	Died	%	No.	Died	%	No.	Died	%	No.	Died	%	No.	Died	%
Third or earlier	91^{21}	5^{3}	5	47^{19}	6^{5}	13	62^{13}	7^{4}	11	242^{12}	69^{10}	32	442^{65}	87^{22}	19.5
Fourth	40^{11}	4^{3}	10	14^{5}	1^{1}	7	42^{11}	5^{3}	12	40^{2}	4^{2}	10	136^{29}	14^{9}	10.3
Fifth	34^{12}	5^{4}	15	23^{17}	6^{6}	26	35^{10}	6^{3}	17	34^{4}	6^{3}	18	126^{43}	23^{16}	18.3
Sixth	24^{5}	8^{5}	33	17^{13}	6^{5}	35	30^{6}	3^{1}	10	20^{1}	2^{1}	10	91^{25}	19^{12}	20.9
Seventh or later†	22^{10}	6^{6}	27	28^{20}	12^{11}	43	56^{11}	19^{8}	34	136^{11}	54^{11}	29	242^{52}	91^{36}	32.6
Total	211^{59}	28^{21}	13	129^{74}	31^{28}	24	225^{51}	40^{19}	18	472^{30}	135^{27}	29	1037^{214}	234^{95}	22.6

* In the cases receiving neither serum nor sulfapyridine, the day of admission is listed
Superscripts represent numbers of bacteremic cases.
† Including cases with undetermined duration.

cases, many receiving the one agent only after the other was apparently failing to bring about prompt relief.

Effect of the Time of Beginning Treatment (Table 8). In accord with previous experience, the death rates in the serum treated cases were lowest in the patients in whom treatment was begun early in the disease. No striking reduction below the expected death rate was noted when serum therapy was first given after the end of the fifth day of illness. This was also true among the patients who received sulfapyridine in addition, since most of the fatal cases listed as having their treatment begun on the fifth day received sulfapyridine alone on that day and were not given serum until the following day, or even later. Among the patients who received sulfapyridine alone, the mortality was high if it was first given after the sixth day, particularly in bacteremic cases. A number of the latter were moribund when treatment was started or they died of complications that had already developed at the time. The lower death rates among those treated earlier with drug alone may be due, in part, to the fact that many severe cases that apparently failed to respond were later given serum and are thus excluded from this category. The high death rate among the patients admitted before the fifth day who received no specific therapy is due, in large part, to the inclusion of many patients whose pneumonia began while they were in the hospital under treatment for other serious illnesses.

The numbers of patients in whom both agents were used are listed in table 9 according to the time relation between the beginning of each kind

TABLE IX

Effect of Time When Each Treatment Was Begun in Patients Receiving Both Serum and Sulfapyridine

	Number of Cases	Bacteremic Cases	Died	Per cent Died
Serum and sulfapyridine begun simultaneously	29	13	4	14
Sulfapyridine given first, followed by serum in:				
Less than 12 hours	38	24	6	16
12 to 18 hours	11	4	2	22
18 to 24 hours	9	7	4	
24 to 48 hours	10	6	4	41
More than 48 hours	8	5	3	
Total *	76	46	19	25
Serum given first, followed by sulfapyridine in:				
Less than 12 hours	12	8	3	25
12 to 24 hours	4	3	3	
24 to 48 hours	4	2	1	42
More than 48 hours	4	2	1	
Total *	24	15	8	33

* Only those patients are included in whom it was felt that the acute pulmonary infection was still active when treatment with the second agent was begun.

of therapy. These data would indicate that the combination of serum and sulfapyridine is most effective if both are begun simultaneously or within from 12 to 18 hours of each other.

The effect on mortality of the extent of lung involvement at the time treatment was begun is shown in table 10. Regardless of the kind of

TABLE X

Mortality in Relation to the Extent of Lung Involvement

Therapy	Pneumonia Involving:						Per cent with More than One Lobe Involved
	One Lobe			More than One Lobe			
	No. of Cases	Died	Per cent Died	No. of Cases	Died	Per cent Died	
Specific serum	158^{42}	12^{9}	7.6	53^{17}	16^{12}	30.2	25.1
Serum and sulfapyridine	54^{32}	9^{8}	16.7	75^{42}	22^{20}	29.3	58.1
Sulfapyridine	152^{27}	11^{5}	7.2	73^{24}	29^{14}	39.7	32.0
No serum, no sulfapyridine	282^{11}	41^{8}	14.5	190^{19}	94^{19}	49.5	40.3
All cases	646^{112}	73^{30}	11.3	391^{102}	161^{65}	41.2	37.7

Superscripts represent the numbers of bacteremic cases.

therapy used, deaths were considerably more frequent when the disease had already extended to involve two or more lobes than when it was still confined to a single lobe at the time when treatment was first given. The difference was much less marked when both serum and sulfapyridine were used than when either was used alone. It is again evident from the large proportion of cases having extensive involvement that more of the worst risks were chosen for treatment with both agents. The death rates were particularly high in the bacteremic cases where more than one lobe was involved. The most favorable results in such cases were obtained with the combination of serum and sulfapyridine. It is noteworthy, also, that among the 33 non-bacteremic cases with more than one lobe involved which were treated with both agents, there were only two deaths (6 per cent), as compared with four deaths (11 per cent) among 36 similar cases treated with serum alone and 15 deaths (31 per cent) among 49 who received only sulfapyridine.

Atypical (Broncho-) Pneumonias and "Secondary" Pneumonias. In previous reports [2a] it was pointed out that patients with pneumococcic pneumonia who have atypical pulmonary consolidation (bronchopneumonia) have a higher mortality in spite of a lower incidence of bacteremia than similar patients who, according to the best available evidence, have typical lobar pneumonia. Furthermore, a considerably larger proportion of the atypical pneumococcic pneumonias are secondary to other serious illness,

while the cases of lobar pneumonia are predominantly "primary"; and, conversely, a much larger proportion of the "secondary" cases have atypical lung involvement, while more of the primary pneumonias have typical lobar pneumonia. This was also true in the present cases, as shown in table 11.

TABLE XI

Atypical (Broncho-) Pneumonias

Type	Serum Treated		Serum and Sulfapyridine		Sulfapyridine		No Serum, No Sulfapyridine		All Cases	
	Number	Died	Number	Died	Number	Died	Number	Died	Number	Died
I	0	—	4^{3}	2^{2}	5^{2}	2^{2}	6^{2}	4^{2}	15^{7}	8^{6}
II	2	1	0	—	1	0	1	0	4	1
III	1	0	5	0	13	3	47^{3}	13^{3}	66^{3}	16^{3}
IV	1	0	0	—	2	0	13^{1}	4^{1}	16^{1}	4^{1}
V	0	—	0	—	1	0	1	1	2	1
VI	1	0	0	—	5	1	23^{1}	6^{1}	29^{1}	7^{1}
VII	2^{1}	1^{1}	1	0	3	0	11	2	17^{1}	3^{1}
VIII	4^{1}	1^{1}	2^{1}	2^{1}	8	2	21^{2}	10^{2}	35^{4}	15^{4}
Others	2^{1}	0	1^{1}	0	21^{1}	8	188^{6}	62^{6}	212^{9}	70^{6}
Total	13^{3}	3^{2}	13^{5}	4^{3}	59^{3}	16^{2}	311^{15}	102^{15}	396^{26}	125^{22}
Per cent died	23		31		27		33		32	
Incidence *	6		10		26		66		38	

Superscripts represent numbers of bacteremic cases.
* Per cent of cases that had atypical pneumonia.

Most of the patients with atypical pneumonia received no specific therapy, but among those who were specifically treated, sulfapyridine alone was used in most cases.

The occurrence of antecedent serious illness in the present series of cases is shown in table 12. We have arbitrarily limited the use of the term "secondary" here, as in previous reports, to those cases of pneumonia which occur as terminal events or during acute episodes of serious chronic illness, and to those cases which follow injuries, operations or parturition. Other cases, including those in patients with chronic ailments or alcoholism and those which follow simple respiratory infections, are classed as primary. The incidence of secondary pneumonias among the present cases is shown in table 13. More than one-half of the atypical pneumonias were secondary, as compared with 7 per cent of the cases of lobar pneumonia. Only a small proportion of the cases of secondary pneumonia were given any specific therapy, and most of those received sulfapyridine, either alone or supplemented with serum. The mortality in the secondary pneumonias was high, regardless of the character of the pulmonary lesion. The numbers of cases are too few to judge the relative effects of different kinds of treatment. In

TABLE XII

Serious Antecedent Systemic Complications in Patients with Pneumococcic Pneumonia, 1938–39

Antecedent Complication	Serum Treated		Serum and Sulfapyridine		Sulfapyridine		No Serum No Sulfapyridine		All Cases
	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died	
Chronic pulmonary disease (bronchitis, bronchiectasis, active tuberculosis, asthma)	5[1]	—	2	1[1]	13[2]	2	25	3	51[4]
Congestive cardiac failure (all kinds)	—	5[3]	6	5[4]	6[1]	6[2]	13	34[4]	75[14]
Coronary thrombosis	—	—	—	1[1]	—	1[1]	—	2	4[2]
Cerebrovascular accidents	—	—	—	—	—	—	5	17	22
Renal failure with or without infection	1	0	3[1]	3[3]	1	0	4	13[4]	25[8]
Malignant tumors: Lung	—	—	—	1[1]	—	—	2	5	8[1]
Malignant tumors: Others	1	—	—	—	1	—	—	6[2]	8[2]
Pregnancy and/or puerperium	2[1]	1	3[1]	—	2	—	1	—	9[2]
Operations or injuries:									
Respiratory tract	3[1]	—	—	—	2	—	4	2	11[1]
Abdominal	4	1[1]	—	—	3[1]	—	19	15[4]	42[6]
Others	4	—	—	1[1]	1	3[1]	9	9[2]	27[4]
Cirrhosis of liver, decompensated	—	2[2]	1	—	—	—	2	2	7[2]
Severe anemia, blood loss	2	1[1]	2	—	—	—	1	3[1]	9[2]
Diabetic acidosis	1	—	2[1]	—	1	—	1	2[2]	7[3]
Acute poisoning other than alcohol	1	—	—	1[1]	1	—	—	1	4[1]
Acute alcoholic intoxication	11[4]	0	6[2]	1[1]	6[2]	4[3]	11	6[2]	45[14]
Delirium tremens	17[4]	9[7]	8[3]	10[9]	9[3]	4[1]	9	7[2]	73[29]

The superscripts represent the numbers of bacteremic cases included.

the specifically treated cases there were 15 deaths among 34 cases with atypical pneumonia (44 per cent) and 12 deaths among 36 with lobar pneumonia (33 per cent). These compare with 50 and 67 per cent deaths among the untreated cases of atypical and lobar pneumonia, respectively.

Effect of Therapy on the Duration of the Acute Disease. The frequency with which recovery * or death occurred at different intervals after the beginning of treatment is shown in table 14. Among the patients who recovered, the average duration of acute symptoms was considerably longer

* Permanent drop in oral temperature below 100° F. with subsidence of other symptoms of the acute infection.

TABLE XIII
"Secondary" Pneumonias

Therapy	Atypical (broncho-) Pneumonias		Lobar Pneumonias		Per cent Secondary
	Number	Died	Number	Died	
Specific serum	6^{2}	3^{2}	15^{3}	5^{2}	10
Serum and sulfapyridine	3^{2}	2^{2}	8^{4}	2^{1}	9
Sulfapyridine	25^{2}	10^{2}	13^{6}	5^{3}	17
No serum, no sulfapyridine	174^{12}	87^{12}	18^{3}	12^{3}	41
All cases	208^{18}	102^{18}	54^{16}	24^{9}	25
Per cent died	49		44		
Per cent secondary	53		7		

Superscripts represent numbers of bacteremic cases.

TABLE XIV
Duration of Symptoms of Acute Pneumonia after the Beginning of Treatment

	No. of Cases	Duration (hours) after Beginning Treatment *							Average Duration† (hours)
		12 or less	12–24	24–36	36–48	48–72	72 or more	Indefinite	
Serum treated	211	97	42	19	10	12	20	11	
Recovered	183	95	40	15	7	8	7	11	21
Bacteremic	38	17	6	6	1	0	1	7	19
Non-bacteremic	145	78	34	9	6	8	6	4	21
Fatal	28	2	2	4	3	4	13	—	145
Bacteremic	21	1	1	4	3	3	9	—	
Non-bacteremic	7	1	1	0	0	1	4	—	
Serum and sulfapyridine	129	33	26	19	10	10	24	7	
Recovered	98	29	24	19	7	8	4	7	23‡
Bacteremic	46	16	10	7	1	4	2	6	23
Non-bacteremic	52	13	14	12	6	4	2	1	23
Fatal	31	4	2	0	3	2	20	—	237
Bacteremic	28	4	2	0	3	2	17	—	
Non-bacteremic	3	0	0	0	0	0	3	—	
Sulfapyridine	225	50	42	50	22	20	33	8	
Recovered	185	37	37	50	18	18	17	8	40
Bacteremic	32	2	8	9	6	2	4	1	50
Non-bacteremic	153	35	29	41	12	16	13	7	38
Fatal	40	13	5	—	4	2	16	—	123
Bacteremic	19	9	4	—	1	—	5	—	
Non-bacteremic	21	4	1	—	3	2	11	—	
No serum, no sulfapyridine	472	77	52	40	31	64	199	9	
Recovered	337	58	39	33	18	45	135	9	96
Bacteremic	3	1	0	0	0	1	1	0	61
Non-bacteremic	334	57	39	33	18	44	134	9	95
Fatal	135	19	13	7	13	19	64	—	158
Bacteremic	27	4	6	1	4	2	10		
Non-bacteremic	108	15	7	6	9	17	54		

* For the cases receiving neither serum nor sulfapyridine, these refer to the time of admission to the hospital, or the onset of pneumonia when it began in the hospital.

† Cases with indefinite termination are excluded.

‡ These four figures refer to the average number of hours after the first dose of sulfapyridine. The corresponding times after the first dose of serum are 18, 20, 18 and 227 hours, respectively.

when sulfapyridine was used alone than when serum was given, either alone or with the drug. Bacteremic patients responded to treatment with sulfapyridine alone more slowly than non-bacteremic cases, but this was not true among those who received serum, with or without the drug. Fatal cases survived, on the average, much longer following treatment with both agents than after either agent given alone. However, a larger proportion of the fatal cases that were treated with sulfapyridine alone died within 12 or 24 hours after the first dose was given. The long average durations of illness in fatal cases are due to the inclusion of patients who died of purulent or other septic complications.

More than one-half of the patients who were treated with serum alone and recovered without complications had a crisis within 12 hours of the first dose, and 87 per cent were free of acute symptoms within 36 hours.

TABLE XV

A Comparison of the Mortality in Horse Serum Treated Cases and in Those Treated with Rabbit Serums in Pneumococcic Pneumonias of Six Types for Which Both Kinds of Serum Were Available

	Patients Treated with Serum (No Sulfapyridine)				Patients Treated with Serum and Sulfapyridine			
	Horse Serums		Rabbit Serums		Horse Serums		Rabbit Serums	
	Number	Died	Number	Died	Number	Died	Number	Died
Type								
I	28^{4}	3^{2}	41^{10}	2^{2}	10^{7}	3^{3}	44^{31}	11^{10}
II	5^{1}	1	24^{10}	6^{4}	2^{1}	1^{1}	20^{11}	3^{3}
IV	4	0	7^{2}	0	1	0	2^{2}	1^{1}
V	11^{3}	2^{2}	9^{4}	3^{3}	4^{2}	0	5^{3}	0
VII	13^{1}	1	11^{4}	2^{2}	2^{1}	0	5^{3}	1^{1}
VIII	11^{4}	0	13^{3}	1^{1}	—	—	6^{2}	2^{1}
Age (years)								
Less than 40	48^{8}	2^{1}	63^{17}	4^{3}	10^{5}	1^{1}	29^{16}	7^{7}
40 to 59	21^{4}	3^{2}	33^{12}	8^{7}	5^{3}	1^{1}	29^{17}	5^{4}
60 or more	3^{1}	2^{1}	9^{4}	2^{2}	4^{3}	2^{2}	24^{19}	6^{5}
Day treatment begun								
Third or earlier	26^{3}	1	51^{15}	4^{3}	10^{6}	3^{3}	30^{13}	2^{2}
Fourth	17^{2}	0	15^{4}	1^{1}	3^{1}	0	5^{2}	1^{1}
Fifth	12^{3}	2^{1}	16^{7}	2^{2}	1	0	16^{13}	3^{3}
Sixth	6	1	16^{5}	6^{5}	2^{1}	0	14^{11}	5^{4}
Seventh or later	11^{5}	3^{3}	7^{2}	1^{1}	3^{3}	1^{1}	17^{13}	7^{6}
Total	72^{13}	7^{4}	105^{33}	14^{12}	19^{11}	4^{4}	82^{52}	18^{16}
Per cent died	10		13		21		22	
Per cent bacteremic	18		31		58		63	
Per cent over 40 years	33		40		47		65	

Superscripts represent the numbers of bacteremic cases included

When sulfapyridine alone was used, 41 per cent of the cases reached a similar stage within 24 hours, and 69 per cent within 36 hours, after the first dose. Among the cases treated with both serum and sulfapyridine, 58 per cent had a critical response within 24 hours and 84 per cent had essentially recovered within 36 hours from the time of the first dose of either agent. It is of interest that 40 per cent of the untreated cases that recovered had a crisis within 36 hours of the time of admission to the hospital.

TABLE XVI

Dosage of Specific Serums

	Serum Alone			Serum and Sulfapyridine		
	Horse	Rabbit	All	Horse	Rabbit	All
Number of patients	73	138	211	19	110	129
Average age (years)	32.6	38.3	36.3	42.1	49.9	48.7
Average dose per patient: Volume (c.c.)	91	47	62	100	59	65
Units (× 1000)	159	195	182	202	262	253
Average number of injections per patient	4.0	3.3	3.6	4.5	3.7	3.8
Average time from first to last injection (hours)	17	12	14	19	13	14
Average total dose per patient (Units × 1000)						
Recovered cases	149	174	165	155	253	246
Fatal cases	251	308	294	380	289	301
Non-bacteremic cases	138	162	152	123	218	204
Bacteremic cases	248	263	259	258	294	289
Average total dose (Units × 1000) according to type of pneumococcus						
Type I	175	159	166	200	244	235
II	209	226	257	278	289	288
III	—	221	221	—	244	244
IV	140	189	171	160	250	220
V	174	213	192	145	226	190
VII	151	296	218	270	418	376
VIII	88	140	116	—	255	255
Others	240	190	192	—	267	267
Number of patients receiving different total doses (Units × 1000)						
Recovered cases						
Less than 50	7	2	9	1	0	1
51–100	15	25	40	4	12	16
101–200	30	62	92	7	28	35
201–400	12	25	37	3	34	37
401 or more	2	3	5	0	9	9
Fatal cases						
Less than 50	0	0	0	0	2	2
51–100	1	1	2	0	2	2
101–200	1	6	7	1	5	6
201–400	4	10	14	1	13	14
401 or more	1	4	5	2	5	7

A comparison of the results of treatment with horse and with rabbit anti-pneumococcus serums is shown in table 15. Only the cases due to the six

common types for which both kinds of serum were available are included in this table. The present data are of interest in view of the recent preliminary report on the use of rabbit serums for Types I, II, V and VII pneumococcus pneumonias at this hospital.[2] The tendency during the present season was to use more of the rabbit serums, particularly in Type II and Type VIII pneumococcic infections. The rabbit serum was used relatively more often in bacteremic cases and in the older patients. In spite of this, the death rates were about the same as among those receiving horse serums, and this was true whether or not sulfapyridine was used in addition.

Dosage of Serums Used (*Table 16*). The average total dose per patient receiving rabbit serum was larger in amount of antibody (units), smaller in volume and was given in fewer injections and over a shorter interval than the average dose of horse serum. This was true, in general, for each of the common types, regardless of whether sulfapyridine was also given. The average potencies of all the serums actually used during this year are given, in units per cubic centimeter, in table 17. The greatest differences in po-

TABLE XVII

Average Potency * of Concentrated Antipneumococcic Serums Used during 1938–39

Type	Horse	Rabbit
I	2035	4085
II	1760	4535
III	—	3100
IV	3600	4970
V	3075	5575
VII	4080	9570
VIII	1550	4420
Others	2000	3880
All	2355	4315

* Expressed in units per c.c.

tency were in the Type II and Type VIII serums, of which the rabbit serums had, on the average, almost three times the concentration of the corresponding horse serums. The average amount of serum used in the patients who also received sulfapyridine was actually greater than in those who received serum alone. The difference in dose, however, was not nearly commensurate with the great difference in the severity of the illness in these two groups of cases, as indicated by the differences in age distribution (table 7) and in the incidence of bacteremia (table 4). An appreciable number of cases recovered after receiving less than 100,000 units and some had a critical response to doses of 50,000 units or less. One-half of the patients who recovered following treatment with serum alone received between 100,000 and 200,000 units. The most frequent dose in the fatal cases was between 200,000 and 400,000 units, even when sulfapyridine was also given. More than two-thirds of those who recovered following treatment with both agents received between 100,000 and 400,000 units of specific antibody.

Serum Reactions (*Table 18*). Immediate reactions, usually considered

TABLE XVIII
Serum Reactions, 1938–39

	Horse Serums		Rabbit Serums	
	92 Patients	380 Injections	248 Patients	862 Injections
Immediate reactions	29 (32%)	43 (11%)	20 (9%)	26 (3%)
Nausea, vomiting, pains, etc.	12	19	5	6
Urticaria, edema	10	15	4	5
Dyspnea, cyanosis, asthma	4	7	6	9
"Collapse"	7	9	6	10
Chills and febrile reactions	35*(38%)	45*(12%)	112 (45%)	156 (18%)
Severe (106° F. or higher)	3	3	7	7
Delayed serum sickness	23 (25%)		47 (19%)	
Severe symptoms	1		2	

* Horse serums furnished by the State Laboratory were used for 165 injections in 40 of these patients. Chills followed 38 injections in 29 recipients of these serums.

to be associated with specific sensitiveness, were less frequent in rabbit serum recipients than in those treated with horse serums. Chills were frequent and occurred somewhat more often with the rabbit serums. The great frequency with which chills were encountered is due, in large part, to the fact that almost all of the serums used were furnished for clinical trial. Most of the lots which gave such reactions regularly or which gave rise to severe reactions were not released for general distribution. Severe chills or marked discomfort from serum sickness occurred infrequently.

TABLE XIX
Dosage of Sulfapyridine Used

	Cases Treated with Sulfapyridine alone					Cases Treated with Sulfapyridine and Serum				
	Recovered	Died	Non-bacteremic	Bacteremic	All Cases	Recovered	Died	Non-bacteremic	Bacteremic	All Cases
Number of cases	185	40	174	51	225	98	31	55	74	129
Average age (years)	44.1	54.1	45.1	48.5	45.8	48.4	49.7	47.5	49.6	48.7
Average total dose (grams)	20.9	18.0	19.5	23.4	20.4	20.1	19.8	13.7	25.3	20.1
Average time from first to last dose (hours)	88	67	80	99	84	81	83	63	95	81
Number of patients who received a total dose of:										
Less than 5 grams	13	12	16	9	25	11	6	9	8	17
6–10 grams	20	10	26	4	30	27	2	19	10	29
11–20 grams	75	7	67	15	82	25	12	15	22	37
21–30 grams	51	5	44	12	56	17	6	7	16	23
31–50 grams	23	2	18	7	25	12	4	4	12	16
51 or more grams	3	4	3	4	7	6	1	1	6	7

Dosage of Sulfapyridine (Table 19). In general, each patient received an initial dose of 2 grams. Severe cases received a second dose of 2 grams, two or four hours later. This was followed by 1 gram every four hours. Occasional doses were omitted because of vomiting. The drug was usually given for two or three days after the symptoms of the disease subsided. In some cases the treatment was begun with 1 gram 4-hourly. The average total dose of sulfapyridine used in all cases was about 20 grams given over a period of about 3½ days. It was about the same in those who received serum and in those who were treated with the drug alone. The average dose in bacteremic cases was larger than in non-bacteremic cases and it was given over a longer period. This was particularly true in the patients who received serum in addition.

Among the patients who were treated with sulfapyridine alone and recovered, 18 per cent received 10 grams or less and 68 per cent received between 11 and 20 grams of the drug. Among the 40 fatal cases in this group, 12 (30 per cent) received only 5 grams or less and another 10 (25 per cent) received a total of from 6 to 10 grams of sulfapyridine. Of the patients who were also treated with serum, 41 per cent of those who recovered were given 10 grams or less, and an additional 24 per cent of the cases received between 11 and 20 grams of the drug. Twenty-three of the 31 fatal cases in this group received 11 grams or more of sulfapyridine. Thus only a small proportion of the deaths can be ascribed to inadequate drug therapy, particularly among those who were treated with the combination of serum and sulfapyridine.

TABLE XX

Toxic Effects of Sulfapyridine Among 354 Patients with Pneumococcic Pneumonia Treated with the Drug Alone or in Combination with Serum

Symptom	No. of Patients
Nausea without vomiting	136
Vomiting	206
Moderate severity (doses omitted)	65
Severe (drug discontinued)	49
Onset after: first dose (1 or 2 grams)	35
3 grams	27
4 grams	36
5 grams	35
6 to 9 grams	45
more than 10 grams	28
Stopped, while drug therapy continued, after:	
less than 12 hours	5
1 day	22
2 days	21
3 or more days	31
Anemia (drop of more than 25 per cent in hemoglobin)	
Acute	7
Delayed	10
Leukopenia (below 5,000) during treatment	9
Renal complication: Hematuria	16
Rise in non-protein nitrogen (more than 25 mg. per cent)	15
Anasarca	2
Marked excitement	22
Drug fever	7
Drug rash	3
Fever (above 100° F. by mouth) following cessation of drug therapy	34

Toxic effects of sulfapyridine in the present cases (table 20) were similar to those reported from most other clinics. In many instances it was hard to determine whether any given symptom was a manifestation of the pneumonia, or of a complication of the disease, or whether it was due to the drug. Those instances in which there was any serious doubt are excluded from the table.

Vomiting was the most frequent symptom. In 15 per cent of all the cases this symptom was so severe that the drug had to be discontinued. While most of the procedures recommended for the relief of this vomiting were tried, they were only occasionally successful, and then gave only temporary relief. In one-half of the cases the vomiting began within 8 to 12 hours and after only 5 grams or less of the drug had been taken. In 10

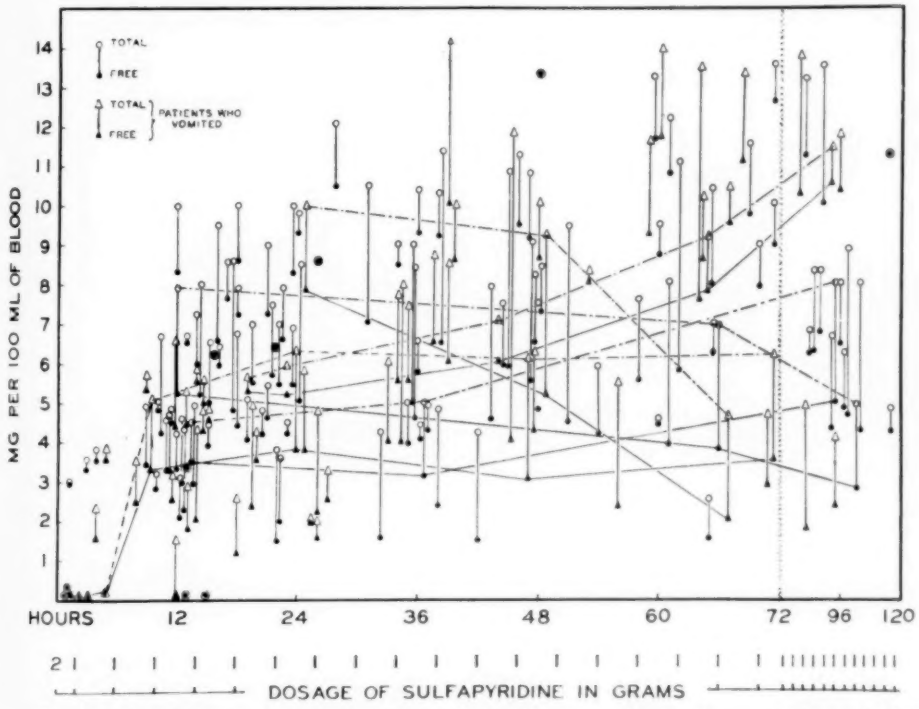

FIG. 1. Blood levels of free and total sulfapyridine in patients who received an initial dose of 2 grams, 1 gram 2 hours later, and then 1 gram every 4 hours. The lines connect determinations made in the same patient at different times.

per cent of the cases the vomiting began soon after the first dose. In some of the cases the drug was given without interruption in spite of the nausea and vomiting, which later subsided after varying intervals while the drug was still being taken. The vomitus in a few cases contained considerable amounts of fresh blood. The acute anemias and leukopenias usually occurred between the second and fifth day. Hemoglobinuria and jaundice did not occur in these cases, nor was agranulocytosis encountered. These reac-

tions were observed in patients who were treated with sulfapyridine during this season for infections other than the pneumococcic pneumonias. Anemias that occurred late in the patients who had purulent complications are not included. This would account for the low incidence of this reaction, since in most of the uncomplicated cases the drug was discontinued within from three to six days. Leukopenias are included here only if they occurred in patients who had leukocytosis before the drug was given. This complication was noted within two or three days after treatment began and thus differs from the agranulocytosis noted in other cases, both in this hospital and elsewhere. On the whole, except for vomiting and occasional severe renal symptoms, the reactions to the drug in the cases of pneumococcic pneumonia were not frequent. This may be due, in part, to the fact that the average duration of treatment was relatively short (table 19) and perhaps, in part, to the close supervision of the cases throughout treatment.

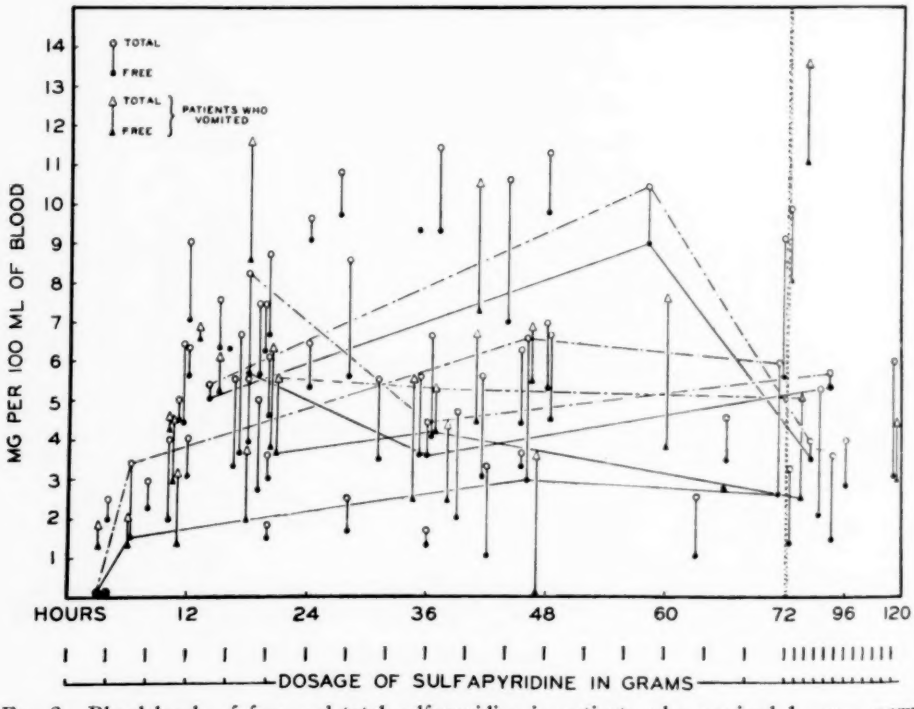

FIG. 2. Blood levels of free and total sulfapyridine in patients who received 1 gram every 4 hours. The lines connect determinations made in the same patient.

Blood concentrations of sulfapyridine [4] varied considerably in different patients even on the same dosage. Although the fluid exchange was not measured accurately, there did not seem to be any regular and close correlation between fluid intake and the concentration of the drug in the blood. The levels attained and the degree of acetylation did not seem to be related to the amount of vomiting. These findings are shown graphically in figures 1 and 2.

TABLE XXI
Postpneumonic Complications

Complication	Serum Treated		Serum and Sulfapyridine		Sulfapyridine		No Serum No Sulfapyridine		All Cases
	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died	
Empyema *	7^{4}	2^{1}	7^{7}	5^{5}	7^{1}	2^{2}	4	3	37^{20}
Sterile pleural effusion	4	—	6^{2}	—	6^{1}	—	4	—	20^{3}
Pericarditis	1	2^{1}	1^{1}	3^{3}	—	1^{1}	—	1	9^{6}
Endocarditis	—	5^{4}	—	4^{4}	—	1^{1}	—	1^{1}	11^{10}
Pulmonary abscess	1^{1}	—	—	3^{2}	1	—	1	3	9^{3}
Meningitis	—	1^{1}	—	1^{1}	—	2^{2}	—	2^{2}	6^{6}
Arthritis	—	1^{1}	1^{1}	1^{1}	—	—	—	1	4^{3}
Peritonitis	2^{2}	—	1^{1}	—	—	—	—	—	3^{3}
Thrombophlebitis	1	1^{1}	2^{2}	1^{1}	2^{1}	1	1	1	10^{5}
Otitis media	3	—	2^{2}	—	2^{1}	—	9	1	17^{3}
Streptococcic infection	1^{1}	4^{3}	2^{2}	2^{1}	1	1^{1}	4	5	20^{8}
Subcutaneous abscess	3^{1}	—	2	—	1	1^{1}	—	2	9^{2}
Atelectasis	4^{3}	—	3	—	2^{1}	—	1	2	12^{4}
Relapse	1	2^{2}	1^{1}	—	1^{1}	3^{1}	4^{1}	—	12^{6}
Jaundice before treatment	6^{1}	1^{1}	8^{4}	—	8^{1}	2^{2}	2	3^{1}	30^{10}
Leukopenia (4,000 or less) before treatment	1	2^{2}	2^{2}	—	—	—	1	—	6^{4}

The superscripts represent the numbers of patients in whom pneumococci were cultured from the blood.

* Among the patients with empyema only 1 in each group recovered without operative intervention other than thoracentesis.

Post-Pneumonic Complications (*Table 21*). Purulent complications and endocarditis were relatively more frequent in the patients treated with both serum and sulfapyridine than among the other cases. This was to be expected from the high incidence of bacteremia.[5] Patients who were admitted for post-pneumonic complications and whose pneumonia was not active at the time are not included in this series of cases. Empyema was the most frequent purulent complication. It is of interest that in the absence of bacteremia it occurred most often in those patients who received either no specific therapy or only sulfapyridine. In the sulfapyridine treated patients who developed septic complications, treatment with the drug in full doses was usually continued for several days in an attempt to eliminate the focus of infection without surgical intervention. As noted in the table, this was not successful, at least in the cases with empyema. In the patients with pericarditis who recovered, this complication was diagnosed on the basis of a definite pericardial friction rub and was considered to be a fibrinous pericarditis without extensive effusion. In those who died, purulent fluid was found in the pericardial cavity. The relatively frequent occurrence of pneumococcic endocarditis in the present series of cases is perhaps dependent on the fact that a considerable number of severely infected patients were kept alive for a longer time than usual with the therapy employed. Hemolytic streptococcus infections occurring during the course of recovery

from the pneumococcic pneumonias were quite frequent. Their occurrence during sulfapyridine treatment or, in some cases, shortly after the drug was discontinued, is of some interest. A number of these patients had blood stream invasion with this organism (table 5). A number of patients with jaundice complicating the pneumonia were treated with sulfapyridine without ill effects. In these cases the drug was discontinued soon after the fever and symptoms subsided.

Of special interest are the cases in which there was a relapse, that is, a recurrence of acute pneumococcic pulmonary infection within a few days and during the patient's stay in the hospital. Only brief mention of the treated cases need be made here. Of the three serum treated cases, two had Type I pneumonia without bacteremia and apparently responded well to treatment. One of these patients later had Type XIX pneumococcic pneumonia with a negative blood culture and recovered without treatment, the other developed a Type V infection with bacteremia and died in spite of specific serum treatment. The third patient was treated with serum for Type VII pneumonia and recovered completely but remained in the hospital under observation for hyperthyroidism. Two months later he developed Type I pneumococcic pneumonia with bacteremia and died in spite of serum treatment. The patient with relapse listed as treated with serum and sulfapyridine received this therapy for a Type I pneumonia with bacteremia which occurred after apparent recovery from a Type III pneumococcus pneumonia without bacteremia which was treated with sulfapyridine alone. The four patients who were treated with sulfapyridine alone had the same type of pneumococcus during the relapse as in the original infection. All were treated with the drug during both episodes. None had bacteremia during the relapse. One had Type I, two had Type III and one had Type VIII pneumococcic pneumonia. One of the Type III cases that had bacteremia when first admitted is included here although he was discharged from the hospital before his reinfection.

Sulfanilamide was used in full doses either alone or as a supplement to specific serum treatment in 138 cases of whom 32 (22 per cent) died. The cases are listed in table 22. Most of the patients treated with this drug alone were due to either Type III or to "higher" types of pneumococci. A large proportion of them (47 per cent) were atypical and only 14 per cent had positive blood cultures. The serum treated patients to whom this drug was given all had typical lobar pneumonia and more than one-half of them had positive blood cultures. The effect of the sulfanilamide on the death rate is difficult to evaluate but it certainly was not very striking.

It is of interest that 10 of the sulfanilamide treated cases developed anemia of a moderate degree (that is, a drop in hemoglobin of more than 25 per cent). This was associated with hemoglobinuria and jaundice in one case. One patient with Type V pneumonia and bacteremia who was treated with sulfanilamide alone developed an extensive drug rash and jaundice

TABLE XXII

Cases of Pneumococcic Pneumonia to Whom Sulfanilamide Was Given in Full Doses Either as the Only Specific Therapy or as a Supplement to Specific Serum 1938–39

Pneumococcus Type	Sulfanilamide Used Alone *		Serum and Sulfanilamide †	
	Recovered	Died	Recovered	Died
I	1	0	9^{2}	2^{2}
II	2^{1}	0	5^{4}	4^{3}
III	12	4	5^{1}	1^{1}
IV	2	1	—	—
V	2^{1}	2^{1}	5^{2}	2^{2}
VI	4	2	1	0
VII	2	0	3^{1}	1^{1}
VIII	4^{1}	1^{1}	1^{1}	1^{1}
Others	43^{4}	10^{4}	5^{3}	1
Total	72^{7}	20^{6}	34^{14}	12^{10}
All "atypical" (broncho) pneumonias	34	9	—	—

Cases to whom sulfapyridine was also given are excluded.
Superscripts represent the numbers of bacteremic cases included.
* These cases are listed in all other tables as untreated, i.e., under "no serum, no sulfapyridine."
† These cases are listed in other tables as treated with serum alone.

associated with hepatomegaly. The death of this patient may have resulted from the toxic effects of the drug, since all the blood cultures taken after treatment were sterile and specific antibodies had developed in the blood.

COMMENT

We have been concerned in this paper with a presentation of the results of therapy and an analysis of the important factors influencing these results. It should be apparent from this study that it is difficult, if not sometimes impossible, to interpret the results obtained in many other clinics when adequate data are not presented and particularly when previous experience with similar cases is not available for comparison. It is natural that a remedy like sulfapyridine, which has a wide application, is inexpensive and involves little effort on the part of the physician would be used much more extensively than an agent like specific serum, which involves considerable conscientious effort, intelligence and experience. No attempt will be made to compare the present cases with those published from other clinics.

The data presented are purposely limited to the pneumococcic pneumonias in adults, since such cases have been studied most extensively in the past and also because they present a more nearly uniform group of infections. To be sure, in many of the cases associated with the so-called higher types of pneumococci, the etiological relationship of the organisms to the disease is not always definite, nor are the clinical pictures presented always

very typical. Both the good and the poor results in many such cases are open to criticism, particularly when no corroborating bacteriological findings from blood, lung or exudates are available. The comparison between serum and chemotherapy in such cases is most unsatisfactory.

It is apparent that both serum and sulfapyridine were highly successful in curtailing the death rate and in bringing about a rapid termination of the symptoms of acute infection. Failures with both kinds of therapy still occur. They are most frequent in aged individuals, in patients treated late in the disease and in those with preëxisting systemic diseases. Delayed deaths also occur from complications of the pneumonia, which are frequently present at the time treatment is instituted and which are not adequately influenced by the treatment.

A number of important factors have not been considered in the present analysis. These include many bacteriological details, particularly the incidence of mixed infection, the effect of persistent vomiting on the results of sulfapyridine therapy and the differences in response to sulfapyridine between cases treated early and those treated late in the disease. Adequate data for the proper interpretation of the significance of some of these factors are lacking. The antibody response in patients treated with sulfapyridine and its possible significance are considered elsewhere.[6] We have also reported separately on the intravenous use of the sodium salt of sulfapyridine in some of the present cases.[7]

Summary and Conclusions

The significant factors concerning the results of treatment in 1037 cases of pneumococcic pneumonia admitted to the Boston City Hospital during the 1938 to 1939 season have been analyzed. Specific serums and sulfapyridine were each found to be effective in reducing the death rate and in bringing about rapid clinical improvement. The combination of serum and sulfapyridine was effective in the cases with the worst prognosis.

Both horse and rabbit serums were effective, but the latter were more concentrated and were used in the poorer risks. Rabbit serums gave fewer allergic reactions than horse serums. Severe untoward reactions from either serum or sulfapyridine were infrequent.

Sulfanilamide was not very effective either when given alone or as a supplement to serum therapy.

On the basis of the results in these cases it is felt that the optimum treatment for the pneumococcic pneumonias should be carried out, in general, as follows: (1) Blood culture and sputum typing should be done as soon as the clinical diagnosis of pneumonia is made. (2) Sulfapyridine therapy should be started at this time. (3) Specific serums should be given to the cases with the worst prognosis as soon as the type is determined. (4) Serum should be given in all cases when there is no definite improvement after 24 to 36 hours of sulfapyridine therapy.

The authors are grateful to the visiting physicians and resident staffs of the various Medical Services and of the Mallory Institute of Pathology for their generous coöperation. They are also indebted to Mildred W. Barnes and Claire Wilcox for technical assistance, to Kathleen Daley and Winifred Doyle for the pneumococcus typing and to Margaret A. Adams and Nancy E. Marean for the chemical determinations.

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RELATIONS BETWEEN AGE AND WEIGHT AND DOSAGE OF DRUGS *

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Because of the existence of individual variability in response to drugs, no method can be devised for determining accurately in advance the proper dosages of drugs for individuals. Average doses, suitable for large groups of adult patients, have been worked out empirically and are printed in pharmacopoeias. This paper is concerned with a survey of methods by which drug dosage might be modified for age and size of individual.

It is natural to proportion dosage according to size of patient, and I suppose it was done even by our Stone Age ancestors. We have today a rule for doing this, Clark's rule, or the weight rule, to take the adult dose as that for a person weighing 150 lbs. and change the dose as necessary in direct proportion to the weight of the patient. The weight rule is represented in figures 1, 2 and 3 by the diagonal straight lines. A person of weight 70 kg. (154 lbs.) is to receive 100 per cent of the adult dose; percentages for those of lesser weights may be read off directly from figures 1, 2 and 3, and for those of greater weights from figure 3, line 1.0.

It is not always possible to ascertain a patient's weight. A number of rules have, therefore, been worked out for estimating the dose from the age in such ways that the computed dose would be very close to that called for by weight. J. Young [71] in 1813 stated that " for children under 12 years old, the doses of most medicines must be diminished in the proportion of the age to the age increased by twelve: for example, at two years old $\frac{1}{7} = 2/(2 + 12)$. At 21 the full dose may be given."

In order to facilitate comparison of the results of using different possible methods of computing dosage, the ages of boys up to 17 years have been set on the bottom line of figure 1 with graduations corresponding to the average weights of boys at different ages, taken from the tables of Davison [18] (for 14 years and under) and Emerson and Manny [30]; the underlying data are shown in table 1. Figure 2 is a corresponding chart for girls. The small drop in weight during the first week of life is disregarded. With this age scale to plot the results of using Young's rule, we find that there is a rough approximation to the average weight rule figures from two years of age up to about the onset of puberty. Bastedo's rule,[4] using the multiplier (age in years plus 3)/30 gives a really beautiful approximation, starting at 1 year, to the average weight rule for children (see figures 1 and 2) and is well worth remembering. The rules of Cowling (age next birthday/24) and Dilling [23] (age/20) are not so good as Bastedo's; they have been omitted

* Read at the New Orleans meeting of the American College of Physicians, March 31, 1939.

† Deceased September 19, 1939.

from figures 1 and 2 to avoid the confusion that would result from plotting five interlacing lines.

Fried's rule,[34] for infants below one year, gives comparatively small doses. Fried introduced the multiplier, age in months/150, and pointed

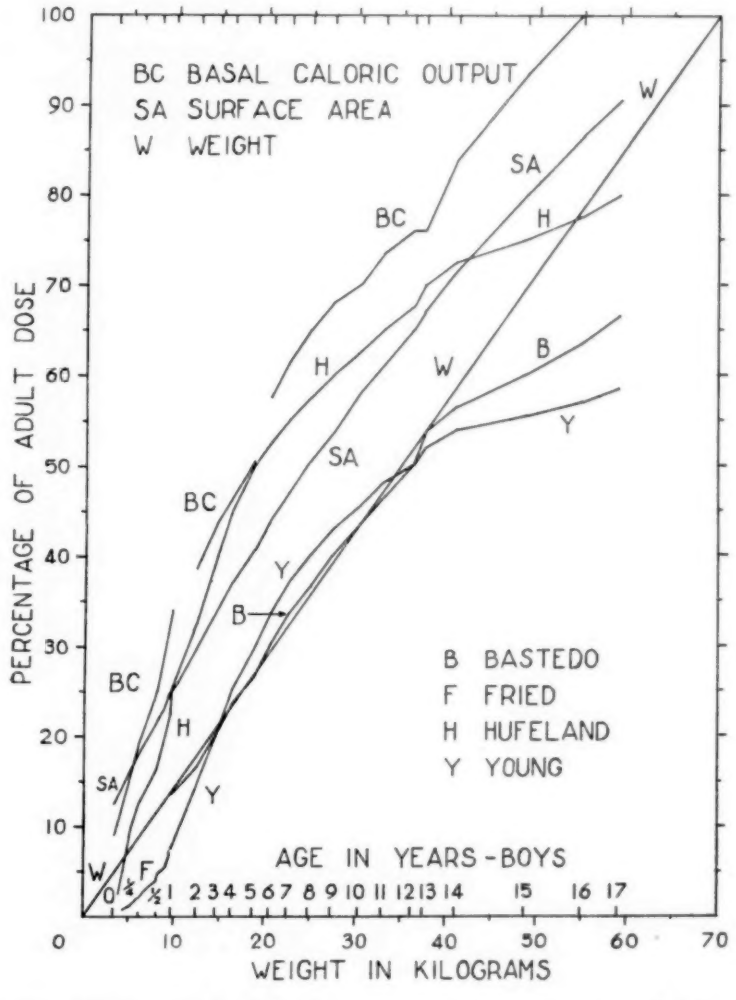
BC BASAL CALORIC OUTPUT
SA SURFACE AREA
W WEIGHT
B BASTEDO
F FRIED
H HUFELAND
Y YOUNG
PERCENTAGE OF ADULT DOSE
WEIGHT IN KILOGRAMS
AGE IN YEARS - BOYS
0 ¼ ½ 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
0 10 20 30 40 50 60 70
10 20 30 40 50 60 70 80 90 100

FIG. 1. Possible bases for proportioning dosage to child age or weight: basal caloric output per 24 hours, surface area, weight with 70 kg. as "adult" weight; Hufeland's method (see text); adult dose multiplied by age in months/150 (Fried, for infants under one year); age in years/age in years plus 12 (Young, for ages below 12 years); (age in years plus 3)/30 (Bastedo).

out that he was thus practically extending Young's rule into the first months of life, since the exact multiplier would be: age in months/(age in months plus 144). All the age rules, except Bastedo's,[4] give doses for the first year of life that are usually below those given by the weight rule. This brings

us to an important point in relation to dosage. It has been and is felt very strongly by many physicians that great caution must be used with regard to dosage for patients at both extremes of life, infancy and old age, and that one should not disregard the obvious truth that a dose too small can be increased, but a dose too large may be irremediable.

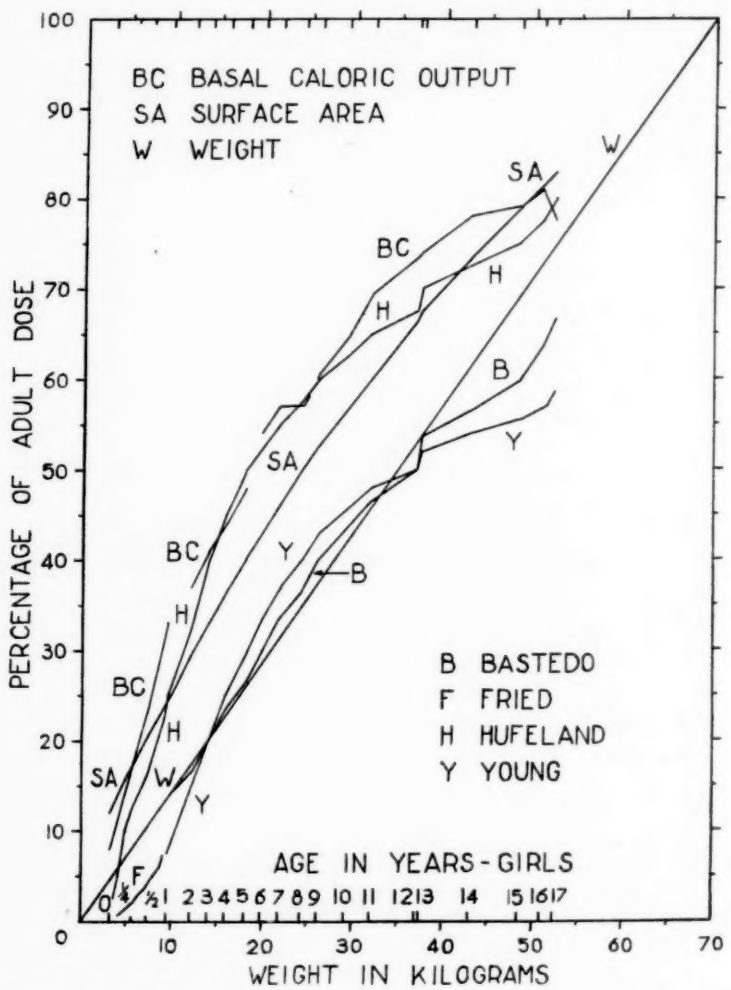
BC BASAL CALORIC OUTPUT
SA SURFACE AREA
W WEIGHT
B BASTEDO
F FRIED
H HUFELAND
Y YOUNG
PERCENTAGE OF ADULT DOSE
WEIGHT IN KILOGRAMS
AGE IN YEARS - GIRLS
0 ¼ ½ 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
0 10 20 30 40 50 60 70 80 90 100

FIG. 2. Possible bases for proportioning dosage to child age or weight: basal caloric output per 24 hours, surface area, weight with 70 kg. as "adult" weight; Hufeland's method (see text); adult dose multiplied by age in months/150 (Fried, for infants under one year); age in years/age in years plus 12 (Young, for ages below 12 years); (age in years plus 3)/30 (Bastedo).

On the other hand there have been, and are today, many physicians of great experience, who, while admitting the force of the argument for caution, incline to the view that infants and children are in proportion to their weight

more tolerant of many drugs than are adults, except possibly during the early days or weeks of life. An expression of this view is shown in figures 1 and 2 in the line drawn from Hufeland's method. Hufeland [31, 41] took as adult dose the figure 40, to be given at age 25. At one-half month of age the dose was to be 1, at one month 2, at two months 4, at three months 5; then increasing every two months by 1, becoming at 11 months 9, at one year 10, at three years 16, at five years 20, at 15 years 30, at 20 years 35; the initial doses always somewhat less, until individual sensitivity had been determined. These figures have been obtained through the kindness of Professor George B. Roth.

TABLE I

Heights, Weights, Surface Areas and 24-Hour Basal Caloric Requirements of Males and Females

Age	Height (nearest cm.)		Weight kg.		Surface Area in Square Meters: DuBois		Surface Area in Square Meters: DuBois-Pfaundler		Basal Caloric Requirement 24 hours			
	M	F	M	F	M	F	M	F	M		F	
Birth	52	52	3.4	3.2	.21	.21	.23	.22	159		145	
1 month	54	53	4.4	4.1	.24	.23	.26	.25	—		—	
2 months	57	56	5.3	4.8	.27	.26	.30	.28	—		—	
3 months	60	59	6.1	5.7	.30	.29	.33	.31	332		307	
6 months	67	66	8.1	7.3	.37	.35	.40	.37	442		401	
8 months	70	68	8.9	8.2	.40	.37	.42	.40	—		—	
12 months	75	73	9.7	9.5	.43	.42	.46	.45	595		584	
2 years	85	85	12.4	12.1	.52	.52	.55	.54	—	(680)	—	(650)
3 years	94	92	14.6	14.0	.60	.58	.62	.60	—	(770)	—	(720)
4 years	99	99	16.3	15.9	.66	.65	.67	.67	—	(820)	—	(780)
5 years	106	105	18.7	18.1	.73	.72	.74	.73	—	(890)	—	(840)
6 years	112	111	20.5	19.9	.79	.78	.80	.79	1010	(940)	950	(880)
7 years	118	116	22.5	21.8	.86	.83	.86	.84	1080	(990)	1000	(910)
8 years	123	122	24.8	24.3	.92	.91	.92	.91	1140	(1040)	1000	(960)
9 years	127	126	27.3	26.1	.98	.96	.98	.96	1200	(1080)	1060	(990)
10 years	133	131	30.3	29.2	1.06	1.03	1.06	1.03	1230	(1135)	1140	(1030)
11 years	137	136	32.9	32.0	1.12	1.10	1.12	1.10	1290	(1170)	1220	(1060)
12 years	142	144	36.2	37.0	1.20	1.22	1.19	1.21	1350	(1220)	1290	(1140)
13 years	145	146	37.5	37.5	1.24	1.24	1.23	1.23	1350	(1220)	1300	(1110)
14 years	151	153	41.0	43.0	1.32	1.36	1.31	1.35	1480		1370	
15 years	160	156	48.7	48.4	1.48	1.45	1.47	1.44	1640		1390	
16 years	165	158	54.9	50.9	1.60	1.50	1.58	1.49	1770		1420	
17 years	169	159	59.0	52.3	1.68	1.52	1.66	1.52	1800		1360	
Adult	173	—	70.0	—	1.83		1.83	—	1760			

N.B. Height and weight values of children from Davison [18] (12 years and under) and Emerson and Manny.[30] Surface area values, "DuBois," calculated from DuBois formula; "DuBois-Pfaundler" calculated from new formula (see text). Basal caloric requirement—values for 12 months and under calculated from data of Talbot, Wilson and Worcester [66] (obtained from females); bracketed values from Lewis, Kinsman and Iliff [47]; remaining values from Boothby, Berkson and Dunn.[10]

Those physicians who believe in the greater proportionate tolerance of the young for drugs have in recent years received support from some laboratory workers. In 1909 the biochemist Benjamin Moore [53] advocated giving doses of drugs in proportion to the ⅔ power of the body weight, or $W^{.67}$, because it approximates a surface area rule. Giving drugs in direct propor-

tion to body weight is in terms of exponents, or powers, to follow the rule $W^{1.0}$. If we use a power less than 1.0, we give the young of a species proportionately larger doses than adult members of the species, and the smaller the power the bigger the proportion of the adult dose that the young receive. This is illustrated by figure 3, in which the doses given by various powers

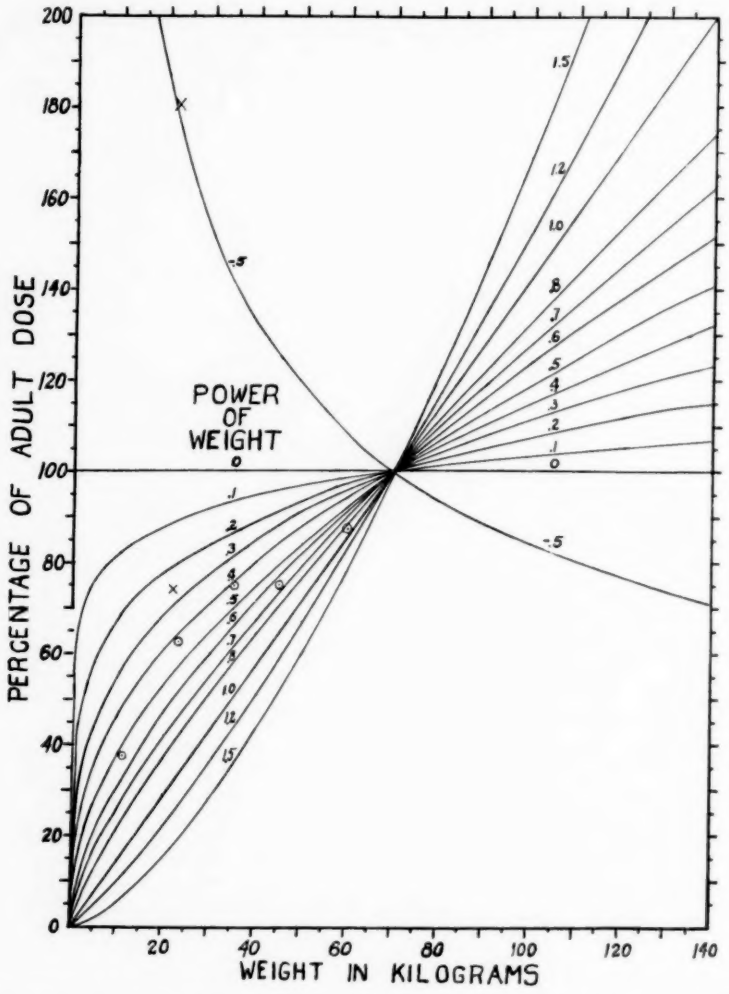

FIG. 3. Percentage of adult dosage that would be given if dosage were proportioned to various powers of the body weight, giving 100 per cent of adult dose to patients of 70 kg. Line 1.0 is that of direct proportion to weight, $W^{1.0}$. Upper x percentage of adult maintenance dose of digitalis for a group of children averaging 22 kg.,[42] possibly maintenance dosage would follow line —.5. Lower x percentage of adult digitalizing dose for same group of children; possibly digitalizing dose would follow line .3. Circles show percentages of dose of sulfanilamide for 70 kg. patient used by Long, Bliss and Feinstone[50] to attempt quickly to initiate blood levels of 10 to 15 mg. per 100 c.c.; appear to average on line .5 (cf. figure 5). Curves calculated from the relation, log dose = 2 + P (log weight — log 70). P = power.

of the weight are shown. If we use the zero power of the weight, or W^0, we give all patients 100 per cent of adult dose, regardless of weight. The rule for $\frac{2}{3}$ power of the weight, or $W^{.67}$, is not shown, but $W^{.7}$ gives a good approximation and also illustrates very nearly the effect of using $W^{.67}$ or $W^{.72}$, a rule advocated by Dreyer and Walker,[25, 26] because of the approximation to a surface area rule. Bazett and Quinby [5] found a satisfactory adjustment by this rule of the anesthetic dose of urethane in the cat. There is evidence, however, that for certain drugs at least, simple mathematical relations of any type based on weight are not likely to hold at the extremes of life (see figure 4, and barbiturates, below).

Returning to figures 1 and 2 we find a surface area rule plotted. This rule follows rather closely the line for a rule on the basis of the $\frac{2}{3}$ power of the body weight, or $W^{.67}$. The values underlying the surface area lines in figures 1 and 2 have been plotted from a new formula, calculated without arbitrary restrictions by the standard mathematical method of multiple regression. It is of interest to note that this method was originally devised by one of the greatest of mathematicians, Gauss,[7] and published in 1821–1826.[64] The DuBois [27] formula: $\log SA = .725 \log H + .425 \log W + 1.8564$ or any other derived from the same nine subjects cannot be used for infants without some commission of the mathematical sin of extrapolation, since the smallest subject weighed 6.27 kg. The data have, therefore, been extended by addition of figures on 12 infants measured by Pfaundler [56] in Germany, by a method very similar, after it was found that multiple regressions computed (Fisher,[33] sect. 29) from the $\log_{10}$ of the two sets did not differ significantly (P. 9, Fisher,[33] sect. 26); this implies that the technic used in the two sects of measurements of the body surface was substantially the same. Pfaundler's 12 infants weighed 2.00 to 5.80 kg. The new formula computed (Fisher,[33] sect. 29) for the whole 21 subjects is:

$$\log SA\ (\pm .004) = .456\ (\pm .084)\ \log H + .509\ (\pm .032)\ \log W + 2.302.$$

This is not by any means a final surface area formula; but proper statistical investigation for homogeneity of the rather numerous groups of surface area measurements in the literature (see Boyd [11]) would be very laborious, and probably without any great improvement resulting. The surface areas computed by the two formulas are given in table 1. The DuBois formula [27] underestimated the surface area of 10 of Pfaundler's 12 infants, the new formula five of 12 with one other almost exact; both formulas underestimated in five of the nine DuBois subjects. Both give 1.83 square meters for the surface area of an adult of height 173 cm. and weight 70 kg., which have been taken as "average male adult" (really about 30 years of age) figures for the purpose of computing values for the surface area lines. Table 1 shows little divergence between results of use of the two formulas except for infants.

Figures 1 and 2 also show lines for proportioning dosage to 24-hour basal caloric requirement, taking 1760 as the normal adult figure. There are

three lines shown. The top line, for six years and up, from the data of Boothby, Berkson and Dunn,[10] is based on results on normal subjects at the first basal metabolic rate reading. The middle line, from two to five years, is based on the extensive material of Lewis, Kinsman and Iliff,[47] on subjects who were studied on different occasions during the growth period. Below two years the figures are calculated from those of Talbot, Wilson and Worcester,[66] for girls, which are probably not particularly different from those for boys at this early age. It will be noted that dosage on this basis would increase very abruptly with age, from about 9 per cent of adult dose at birth to 25 per cent at six months, 50 per cent at about five years and 75 per cent at 11 years (boys, girls 13).

The possible importance of basal caloric output in connection with drug dosage has been pointed out particularly for morphine.[37] Morphine is generally considered poorly tolerated in infants and old people. In old age and during the first few weeks after birth dosage on the basis of basal caloric output would be lower than at intermediate ages, but on this basis would become relatively high at six to 12 months of age (figures 1 and 2), so that the danger from morphine is probably connected with some other factor than basal caloric output, possibly with a high sensitiveness of the respiratory center. Use in the mother late in labor, within less than about four hours prior to delivery, is likely to cause respiratory depression in the child delivered.[60] Bastedo [4] states that he has seen a child of one year "doped" by gr. $\frac{1}{20}$ of powdered opium, or only about gr. $\frac{1}{200}$ (0.3 mg.) morphine, or about gr. $\frac{1}{160}$ morphine sulfate. Schlossmann [57] says, "in infants symptoms which threaten life may appear after one drop of opium tincture" and recommends that neither morphine nor any preparation containing opium be given before the fourth year of life" without the most urgent indications." An important practical point to emphasize here is the great natural individual variability in response to drugs. Serious respiratory depression, or actual apnea, may occur in an occasional patient of any age even from what had been thought a very safe dose of morphine. Caution is necessary in giving morphine to any patient whose susceptibility to morphine has not been determined, and especially so in the young and the aged. Though it is not the controlling factor, basal metabolic rate is of some importance. Ordinary morphine dosages are considered dangerous in markedly hypothyroid patients. Guedel [37] states that a patient in postoperative thyrotoxin storm will destroy gr. $\frac{1}{4}$ (16 mg.) morphine sulfate in one or two hours, while in the aged gr. $\frac{1}{6}$ (11 mg.) will still be effective after six or eight hours. In some old people gr. $\frac{1}{8}$ (8 mg.) may be a dangerous dose of morphine sulfate. Thus, it seems that, taking as standard the official U. S. P. dose of 8 mg. (gr. $\frac{1}{8}$) and regulating the dosage of morphine for infants, children or the aged, in direct proportion to weight, may result in giving a dangerous dose.

Codeine phosphate is given by Pfaundler and Schlossmann [57] in infants

4 to 12 months of age in doses of 1 to 5 mg. Their extensive table of drug dosage for infants and children merits study.

The dosage of antiluetic drugs is commonly made larger for children than for adults in proportion to weight. Thus, children may be given 15 mg. neoarsphenamine per kg. after the preliminary small initial doses,[18] while the corresponding doses for adults are only about 9 mg. per kg. (dose of 0.6 gm.). Even greater differences are made in one large clinic [13] as shown in table 2 for "old arsphenamine," bismuth, and mercury salicylate, infants

TABLE II

Dosages of Antiluetic Drugs, Vanderbilt Clinic, New York [13]

Drug	Alternate Plan		Infants and Children			
	Men	Women	Birth to 6 months	6 months to 1 year	1 year to 6 years	6 to 14 years
Old Arsphenamine						
Initial dose	0.2	0.15	0.075	0.1	0.1	0.15
Fourth week 1st course	0.3	0.2	0.1	0.15	0.15	0.2
Seventh week 1st course	0.4	0.35	0.1	0.15	0.2	0.25
2nd course	0.5	0.4				
Mercury Salicylate						
Initial	gr. 3/4		gr. 1/10	gr. 1/4	gr. 1/4	gr. 1/4
Maximum	gr. 1-1/2		gr. 1/2	gr. 1/2	gr. 1/2	gr. 1
Bismuth *						
Initial	1 c.c.		1/4 c.c.	1/2 c.c.	1/2 c.c.	1 c.c.
Maximum	2 c.c.		1 c.c.	1 c.c.	1 c.c.	1-1/2 c.c.

* Based on preparations containing 50 mg. of elemental bismuth per c.c.

receiving 20 per cent of the maximum adult dose of old arsphenamine, 33 per cent of that of mercury salicylate, and 50 per cent of that of bismuth. It is interesting to compare these with the dosages indicated by various rules in figures 1 and 2. Because of the step-like increases of antiluetic dose with increasing age, it is difficult to formulate the rate of increase.

A number of other drugs seem to be tolerated better by children than would be expected from the results of applying any of the commonly used dosage rules. Thus, Bastedo [4] states that "the child's dose of a cathartic or belladonna or arsenic approaches that of an adult." He cites two interesting paired observations in human pharmacology: (1) "we have seen the same amount of belladonna given to a father and to his son six years of age with equal effect," and (2) "a child of three not one whit more affected by a grain of calomel than was her mother by half the dose." Pfaundler and Schlossmann [57] show the dose of castor oil for infants 4 to 12 months of age as 5 to 10 c.c.; the British Pharmacopoeia (1932) gives the adult dose range as 4 to 16 c.c.

Atropine is sometimes administered practically to the limit of tolerance to

infants in pyloric stenosis and to adults in postencephalitic Parkinsonism. Assuming complete absorption, which is here rather unlikely, infants of two to four weeks, averaging about 3.9 kg., may possibly tolerate total daily dosage of about 1.5 mg.,[60] 16 to 20 per cent of the corresponding adult figure, also producing symptoms of beginning atropine poisoning, which is 7 to 9 mg.[36] Infants thus may possibly tolerate two or three times as much atropine as would be expected on the basis of weight.

In pharmacological experiments it is common, despite the warnings of Moore,[53] Dreyer and Walker,[25] Bazett and Erb,[6] and others, to proportion dosage of drugs to the weight of the animal, assuming that unusual results, at least within the same species, are accountable for on the basis of individual variation. My satisfaction with this procedure was finally upset by the results shown in table 3, obtained by titration of morphinized rabbits by ear vein with ouabain solutions to the end point of cardiac stoppage.[21]

TABLE III

Preliminary Study of Effect of Rate of Injection and of Body Weight on the Lethal Dose of Ouabain in the Male Rabbit

Number of Rabbits	Injection Rate, mg. per kg. per min.	Mean Wt. in kg.	Mean Lethal Dose, mg. per kg.	Standard Deviations		Conclusions
				Wt.	Dose	
10	.001	1.59	.261	.20	.071	Effect of injection rate not marked
10	.002	1.87	.198	.28	.021	
10	.003	1.62	.242	.36	.042	
10	.004	1.75	.217	.24	.039	Small rabbits relatively more tolerant than large
10	.006	1.49	.238	.12	.056	
10	.008	1.68	.220	.32	.032	
10	.010	1.54	.243	.10	.047	
10	.010	2.65	.141	.22	.030	
10	.012	1.36	.246	.12	.038	
10	.016	1.61	.230	.19	.043	
10	.032	1.42	.304	.26	.045	Effect of weight obscured by that of injection rate
10	.064	1.42	.398	.26	.068	
10	.128	1.66	.628	.18	.071	
10	.256	1.77	.973	.32	.169	

A glance at table 3 shows that wherever there is an increase in the average weight of the rabbits in a group, the average lethal dose goes down, conspicuously so with the groups of small and large male rabbits on rate 10; on use of larger numbers of animals the difference became less conspicuous, but remained in the same direction. Table 3 also makes clear the increase in mean lethal dose at very rapid rates of injection. The main object was to investigate the effect on lethal dose of rate of injection, which has been found very important in determining the "cat unit."[2, 67] As frequently happens in research, we found something we were not looking for, a weight effect in this instance.

I was fortunate enough to be able to enlist the aid of Dr. C. I. Bliss in the analysis both of these rabbit data and of data obtained previously by Dr. B. J. Vos [67] at the University of Chicago on cats of both sexes and weights, 1.26 to 5.07 kg. Using the logarithms of the observed results and the method of Fisher,[33] sect. 29, it was found that the smaller animals were, in both species, relative to their weight, more tolerant of cardiac glucosidal preparations than the larger animals. The powers of the weight involved were as follows: 130 cats on digitalis 0.89 ± 0.06, less than 1.0, but not significantly so; for 61 cats on digitoxin 0.77 ± 0.08, and for 153 cats on ouabain 0.79 ± 0.05, both significantly less than 1.0. For 204 rabbits we found [21] the dose proportional to about the 0.6 power of the weight, $W^{.573 \pm 0.058}$, to be (a bit fussily) exact. Here the 0.058 is the standard deviation of 0.573, the difference from 1.0 is 0.427, and this difference is $0.427/0.058 = 7.3$ standard deviation, from which we can calculate that the probability is less than 1 in millions of our being wrong in assuming that on the average small rabbits are, in proportion to weight, more tolerant of ouabain than large rabbits, at least within the experimental weight range, 1.02 to 3.64 kg.

It is interesting that Dr. Bliss [8] found in analysis of data obtained by Campbell in the silkworm that the larger silkworms were more tolerant of arsenic in proportion to their weight than the smaller animals, so that the size factor for time of death could be stated as $W^{1.511 \pm 0.089}$. Finding in the size factor an exponent greater than 1.0 is infrequent in the literature of the subject; the work of Falck on strychnine, however, supplies a parallel (figure 4). Dreyer and Walker [25] were impressed by finding in the standardization of diphtheria toxin in guinea pigs that " when the dose per 100 gm. of weight is made the same in light and heavy groups of animals of the same species the lighter animals survive for a much longer period than do the heavier. The explanation of this difference in death time is to be sought in a comparison of the doses calculated in relation to the surface. It is then seen that the dose thus calculated is much smaller in the lighter animals than in the heavier group." They reported [25] after examination of the literature that this was no isolated instance, and that " we have not up to the present met with any exception in the case of mammals and birds " to the general rule that smaller animals within the same species were in proportion to their weight more tolerant than larger ones. They list among the substances for which this appeared to hold good, either for effect on time of death or lethal dose (or possibly other effects) observations by various workers on arsenic trioxide, codeine, physostigmine and potassium chloride in the rabbit; various snake venoms in rats, rabbits, guinea pigs and cats; epinephrine and tetanus toxin in the mouse; and caffeine in dogs, cats and rabbits.[25] The methods of calculation are shown in considerable detail in a second paper.[26]

Dreyer and Walker [25] further point out that while examples can be found of greater tolerance per kg. to drugs or other toxic agents in small species,

e.g., the mouse, than in larger species, e.g., the guinea pig, the opposite phenomenon has also been observed (figure 4).

Clark [16] has recently reviewed the same subject. He appears to me, after examination of the references quoted, to be in error in his statement that "large mice are less susceptible than small mice to both neoarsphenamine and to aconite." Clark [16] has, I believe, in the case of aconite put a wrong

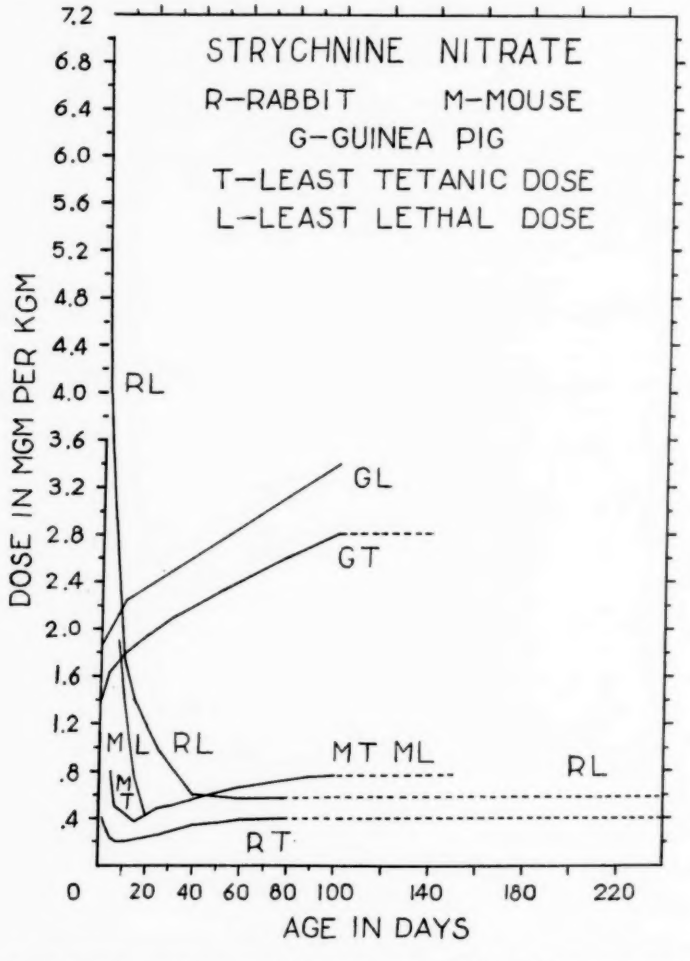

FIG. 4. In different species completely different relations between age and effective dosage of drugs may be obtained. Though mice are smaller than guinea pigs, their tolerance for strychnine is less in proportion to weight (Falck, 1884, 1885).

interpretation on a confusing report by Broom, Burn, Gaddum, Trevan and Underhill.[12] The conclusion drawn by the writer from study of this report is that the authors intended to state that they felt they had not established a significant difference in tolerance for aconite per gram, between small mice and large mice, the observed difference being considered a difference in colony resistance to aconite.

With regard to neoarsphenamine, which is given in somewhat larger dose per kg. to children than to adults, Durham, Gaddum and Marchal [28] state that "so far as our evidence goes, it would appear that, in immature mice, sensitiveness increases with age at such a rate as almost to neutralize the effect of increase in weight. On the other hand, in mature mice, from 20 gm. upwards, resistance apparently ceases to diminish at such a rate, so that some adjustment of dose by weight becomes necessary; and adjustment by simple proportion to weight seems likely to be as accurate in that range as that given by the use of any other formula."

If we have a definite end-point producible by a drug such as a measurable blood concentration of the drug, as with sulfanilamide, or rather sudden dramatic therapeutic improvement, as with digitalis in congestive heart failure, or fairly definite toxic symptoms, as with digitalis, or atropine, we can record the dose, daily, accumulated, or single, as the case may be, that was responsible in each patient for producing the result and by plotting against weight in various ways obtain some idea as to types of mathematical relation between weight and dose. A rather frequent finding, in view of fairly numerous references to dosage being properly proportional to various fractional powers of the body weight, appears to have been that plotting log dose against log weight gives results not significantly different from a straight line, at least over fairly considerable ranges of weight (figure 5). Where this is the case, the slope of the line is the power of the weight involved, and can be measured approximately from the diagram (vertical/horizontal intercept), or calculated by the method of least squares (Snedecor,[64] tables 6, 7).

A recent report on sulfanilamide by Long, Bliss and Feinstone [50] enables the calculation of mathematical relations between body weight and dosage advised to initiate or to maintain certain blood levels. Dr. Long has kindly pointed out that the same daily dosage may maintain different blood levels in the same patient, depending on whether or not there is restriction of fluid intake. The results of the calculations are shown in table 4 and figure 5. They suggest that therapeutically equivalent dosages of sulfanilamide are proportional to a power of the weight less than 1.0, and possibly around 0.5 to 0.8.

While logarithms are convenient for the mathematical analysis, their significance is not readily apparent. Use of figure 3 makes clearer just what is meant by proportioning dosage to powers of the weight. From this it can be seen at once, for example, that proportioning the dose to $W^{.5}$ would mean that the average 100 kg. man (220.5 lbs.) should receive approximately 120 per cent of the adult dose (i.e., for 70 kg. weight). For estimating the power of the weight to which dose may be proportional, figure 3 is obviously not nearly so useful a type of device as figure 5, however.

The table of dosages used at Children's Hospital,[15] Iowa City, shows infants and children more tolerant of epinephrine in proportion to their

TABLE IV

Relations between Body Weight and Therapeutic Dosages of Sulfanilamide in the Human Species

Information Used [50]							Therapeutic Dosage* Proportional to
Initial dose * used in establishing quickly a blood level of 10 to 15 mg. per 100 c.c., for weight of							
kg.	70	60	45	35	23	11	
dose, grams	4.8	4.2	3.6	3.6	3.0	1.8	$\frac{W^{.48}}{1.6}$
mg. per kg.	69	70	80	103	130	164	
Daily total dosage * used in keeping up blood levels of 5 to 10 mg. per 100 c.c.							
kg.	70	60	45	35	23	11	$\frac{W^{.60}}{2.1}$
dose, grams	5.4	5.4	5.4	4.2	3.6	1.8	
mg. per kg.	77	90	120	120	157	164	$\frac{W^{.74}}{3.2}$
Omitting first two dosages							

* Somewhat dependent on urinary excretion, and restriction of fluid intake.[49] Dose refers to total amount of drug, not to amount per kg.

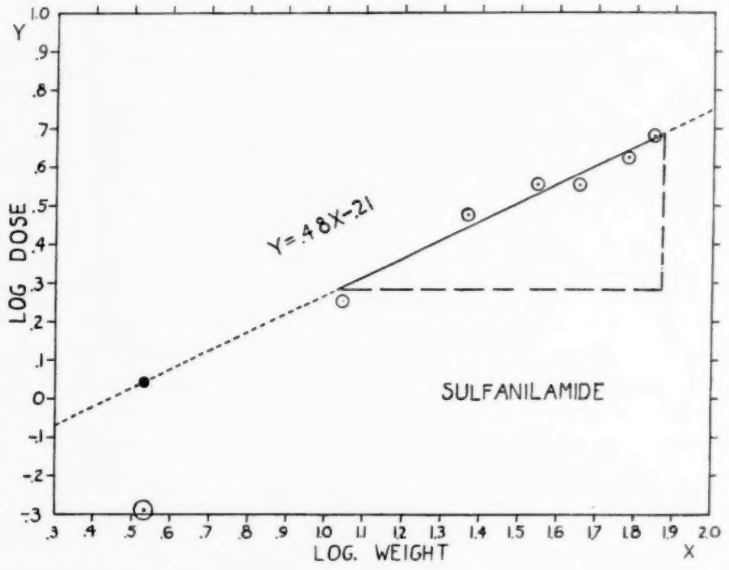

FIG. 5. Graphic test of linearity of relation of log (initial dose in grams of sulfanilamide used in bringing about a blood level of 10 to 15 mg. per 100 c.c.) to log weight in kg. The power of the body weight to which dose may be proportional is given by the slope of the solid line. Extrapolation to find the initial dose for a 3.4 kg. child gives the solid circle value, .04 antilog 1.1 grams; the extrapolation apparently fails, as Dr. Long [50] gives the desired dose as 0.51 grams (0.15 gram per kg.).

weight than adults. The hypodermic doses given are: at 6 months 3 minims (0.2 c.c.), at 18 months 4 minims, at 3 years 6 minims, at 5 years 7 minims, adults 7 to 15 minims (average thus 11 minims). Plotting a similar diagram to that for sulfanilamide in figure 5, the dosage of epinephrine comes out proportional roughly to the 0.6 power of body weight.

Bodansky and Duff [9] have found immature rats tolerate dosage of thyroxine rapidly lethal to mature rats.

The effective doses of digitalis in adults seem to be close to those necessary in children, and the daily maintenance dose in a child may be more than that required by the average adult. Withering [69] noted that nausea generally appeared, presumably in adults, when about 30 grains (1.94 gm.) altogether had been given. McCulloch and Rupe [52] gave children of 1 to 11 years with normal hearts doses of digitalis every four hours. Vomiting occurred after 4 to 20 doses in 17 out of 36. The amount required to produce emesis in these 17 cases averaged 17 c.c. of tincture, or 1.7 gm. of leaf, and assayed as 17 "cat units." The digitalizing dose for an adult averaged in Eggleston's series [29] about 2.2 gm. and in Pardee's [54] about 2.4 gm. in terms of good standard leaf of the time, of which 0.1 gm. was considered a "cat unit." (Incidentally, owing to recent change in U. S. P. standard for digitalis, a "cat unit" is now about 65 mg., apparently for a good standard leaf [70]; even more interesting, a "cat unit" is bigger if got by the 30 to 55 minute death times of the Magnus modification [22] of the cat method, which some use, than if done by using the death times around 90 minutes of the Hatcher-Brody method (Alday Redonnet [2]),[40] and less with ether anesthesia than with some other sorts,[59] and it is somewhat common for authors to omit to state what sort of "cat unit" they have.) Subject to these reservations, we may make tentative comparisons of doses for adults and children. The average 70 kg. adult may require about 33 mg. per kg. for digitalization. Jacobsen and Davison,[42] working with a group of children of 16 to 28 kg. (average 22 kg.) found the digitalizing dose of a leaf, probably of good standard potency,[35] average 1.7 gm., or 78 mg. per kg. To find the approximate power, P, of the weight to which the digitalizing dose of digitalis might be proportional, we may use the formula:

$$P = \frac{\log \text{adult dose} - \log \text{children's dose}}{\log \text{mean adult wt.} - \log \text{mean wt. of the children}}$$

$$= \frac{\log 2.3 - \log 1.7}{\log 70 - \log 22} = \frac{.36 - .23}{1.85 - 1.34} = .25$$

Turning to the question of daily maintenance dose of digitalis, we may use the following data. Jacobsen and Davison [42] found the maintenance dose for children average 200 mg. daily and Davison after further experience includes this figure in "The Compleat Pediatrician." [18] From Pardee's figures [54] the average for adults may be calculated as 111 mg.

Using the same formula as before:

$$P = \frac{\log 111 - \log 200}{.51}$$

$$= \frac{2.05 - 2.30}{.51} = \frac{-.25}{.51} = -.5$$

We thus reach the very interesting tentative conclusions, that the average "digitalizing dosage" of digitalis leaf is greater for children in proportion to their weight than for adults, and that the average daily maintenance dosage for children of about 22 kg. average weight is not only greater than that for adults in proportion to weight, but greater in absolute figures. The digitalizing dosage may be proportional to $W^{.3}$ approximately, and maintenance dosage of $W^{-.5}$ approximately. Figure 3 does allow here of estimating these powers directly, since there is only one point to plot in each case, the second being always at the "big intersection," simply by plotting percentage of adult dose (x) against child weight and taking as the power that for the nearest curve. These are very rough estimates, from admittedly inadequate data, but it is hoped they will stimulate further observations.

Eggleston [29] and Pardee,[54] who worked with adults, and Jacobsen and Davison [42] from experience with children, found no outstanding relation between dosage and body weight within their groups of patients. This may have been due to the small numbers of cases worked up, and to natural variability of results, enhanced by use of different preparations (biologically standardized) in different groups of patients.

Dreyer and Walker [25, 26] seem to have overlooked Falck's early (1884, 1885) observations,[32] to which Clark [16] draws attention. Falck [32] made observations on the effect of age on least observed tetanic and lethal doses of strychnine during at least the first 100 days in the life of the guinea pig, mouse and rabbit. The results are shown in figure 4. The least observed lethal dose per kg. for the rabbit was highest at birth and diminished rapidly, indicating a size factor less than 1.0. The tetanic doses for the rabbit and mouse, and the lethal dose for the mouse at first diminished with increasing age, and then increased, apparently reaching eventually a plateau. Both the tetanic and the lethal doses per kg. for the guinea pig increased from birth on for at least 100 days; in the rapidly growing guinea pig, which has a more advanced neuromotor mechanism at birth than either mouse or rabbit, there seems thus to be clearcut evidence of a size factor greater than 1.0. The evidence from animal experiments is hence somewhat contradictory, but is certainly such as to make one very cautious about giving strychnine to children. Strychnine is not important as a drug for children, but Aikman [1] says, "strychnine poisoning with brightly colored sugar-coated cathartic and tonic tablets causes more deaths in children than any other poison" (see also Priest [59]). The lethal dose for a child may be very small; a boy of 3½ years has been killed by a dose estimated as 2 or 3 mg. (gr. 1/32 or 1/20) [48]; an adult has been killed by 36 mg., or a little over ½ grain of strychnine hydrochloride.[48]

It is of particular interest to consider next the size factor for barbiturates, among which are apparently the most effective strychnine antidotes. Clear clinical reports have established the life-saving value of sodium amytal [43, 59] and pernoston,[44] and the prompt cessation of the painful and

potentially traumatizing [14, 20] strychnine convulsions when these drugs were given by vein in human cases. A number of other barbiturates, especially [3] pentobarbital (nembutal), when given by vein have been found in the laboratory to suppress strychnine convulsions,[19, 20] and the antagonism is demonstrable even in the spinal cat.[58]

Barbiturates are generally considered well tolerated by children. Clark [16] found the results of Bazett and Erb [6] on the anesthetic dose of pentobarbital in cats and dogs to follow the relation approximately $W^{.67}$, though Bazett and Erb [6] did not consider so simple a relation sufficient. Donald and Raventos [24] have recently reviewed the somewhat contradictory literature on the size factor for barbiturates. The need for caution during the early days of life is emphasized by their report on the barbiturate sodium evipal. Giving 20 mg. per kg. by vein in pigs, they found the duration of narcosis in pigs six months old averaged about 20 minutes, in those 10 to 80 days old about 12 minutes, but in pigs two to four days old rose to 50 minutes. The new-born were thus highly susceptible; the higher susceptibility wore off at about 10 days of age and began to rise somewhat at about three months of age. There was considerable variability among individuals of the same age. Pearcy and Weaver [55] considered that old dogs as well as young dogs were less tolerant of barbital than dogs of intermediate age, which emphasizes sensitiveness at both ends of the age scale.

Comparing Falck's results with strychnine [32] (figure 4) with those of Donald and Raventos [24] with sodium evipal, one finds Clark's conclusion [16] inescapable: " at present it is impossible to enunciate general laws regarding the relation between dosage and body weight, since completely different relations appear to be obtained with different drugs," and, one may add, in different species.

Why children require or tolerate in proportion to their size higher dosage of some drugs than do adults cannot at present be explained. Dreyer and Walker [25, 26] considered blood volume which they found proportional to surface area, or about $W^{.72}$, of paramount importance. One must, however, take into account several other possible factors, such as larger proportionate average basal metabolic rate, daily urinary output, and weight of liver and other organs concerned with destruction or conjugation of drugs.

The liver in a man 20 to 30 years of age averages, according to Roessle and Roulet,[62] 1587 grams; in a woman, 1371 grams, or 86 per cent of that of the male. Assuming a drug to be entirely destroyed in the liver, and livers to have the same destructive capacity per gram liver tissue at all ages, the new-born, with livers averaging 78 grams, according to Coppoletta and Wolbach,[17] would tolerate about 5 per cent of the dose for the adult male, or substantially the proportionate dose indicated by their body weight, according to the weight rule (figures 1, 2). Several authorities give much higher liver weights at birth than 78 grams, but this figure of Coppoletta and Wolbach [17] has been preferred, since they definitely excluded livers showing pathological changes. The average liver weight increases at first slightly

and later definitely more rapidly than the body weight, so that using the same table [17] of liver weights we should give a dose at six months of 13 per cent, at two years 25 per cent, at six years 40 per cent, and at 12 years 58 per cent of adult dose, all somewhat in excess of the proportions indicated by the weight rule of figures 1 and 2, but not so great as those indicated by surface area. Thus, in children the somewhat disproportionately rapid growth of the liver may possibly be a factor in increasing tolerance to some of the drugs, such as quinine, barbital and phenobarbital, which are partly destroyed or detoxicated in the liver, to the more unstable barbiturates which are almost wholly destroyed in the body, and to arsphenamine, the arsenic from which is excreted chiefly by way of the bile into the feces.[65]

In the case of sodium and ammonium mandelates used therapeutically, the daily dose is sometimes given as 1 gram per 100 c.c. of previous 24 hours urine, the object being to obtain urinary concentrations of 0.5 to 1.0 per cent of the drug. This may work out at about 4 grams for an infant, whose urine volume may average 400 to 600 c.c.,[46] and practically adult dose of 12 grams for a 12 year old child, whose urine volume may average 1200 to 1500 c.c.,[46] quite in the adult range. This factor also affects the dosage of sulfanilamide, the dose of which is sometimes given as " for adults ⅓ grain, for infants 1 grain per pound of body weight." In proportioning dosage of drugs on the basis of urinary output, it should be remembered that the fluid intake during the first day of life may be only a few c.c., during the second day only about 100, the third 250, the sixth 400, the fourteenth 500 c.c.[57]; even assuming about 40 per cent of this to appear as urine, the volume seems insufficient to permit any great amount of drug excretion through the kidney during the early days of life. The 24-hour urine volume is, moreover, subject at all ages to tremendous fluctuations [45] from day to day, being affected by fluid intake especially, by temperature of air and body, humidity, clothing, diet, etc. The lungs and skin always have primary liens on the water provided in ingested food and drink. The extraordinary variability of basal 24-hour urinary volume in c.c. is well illustrated by coefficients that have been given for calculating this as averaging 1000 times surface area (table 1), but with a minimum coefficient of 400 times and a maximum of 1500 times.[61] Thus, for a boy of 9 years of age the basal 24-hour urine might average 980 c.c., but vary from 390 to 1470 c.c., or even larger amounts with excess fluid ingestion. The high average ratio of urinary output to body weight suggests that older infants and children should have, as a rule, a very good tolerance for many drugs excreted largely or chiefly through the kidney,[65] such as quinine, phenobarbital, bismuth, mercury, atropine, mandelic acid, sulfanilamide. We should expect the new-born on the other hand to be rather sensitive to drugs excreted mainly in the urine.

The antimalarial dosage of quinine sulfate suggested by the Malaria Commission of the League of Nations [38, 51] is 1.0 to 1.2 grams (15 to 18 grains daily) and recently by the U. S. Public Health Service 20 grains (1.3 grams) daily. An article by Ross and Alcock [63] says of quinine " children

can be given a larger proportion by body weight than adults, say twice as much." On this basis a child of 12 with malaria would be given the adult dose, say 1.0 gram, daily; at 5 years 0.5 gram daily, and 1 year 0.2 gram daily; Pfaundler and Schlossmann [57] recommend 0.01 gram (⅙ grain) quinine hydrochloride per month from 4 to 12 months of age as daily dosage; larger doses are recommended by some other workers.

The barbiturates are partly detoxicated in the liver and partly excreted in the urine.[65] With barbital 75 per cent and with phenobarbital 10 to 40 per cent may appear in the urine unchanged, with the newer and briefer-acting less or none. Children are generally considered to tolerate phenobarbital very well, which is perhaps explicable on the basis of somewhat higher proportion of liver tissue and greater urinary output. On the other hand, the same reasons would cause one to think that strychnine should be well tolerated by children, and the evidence rather points to strychnine being even more dangerous in children than in adults.

Discussion

There seems to be enough evidence available to show that it is not sufficient to teach that dosage of drugs for children should be determined by direct proportion to weight, or by use of simple rules. The main points to emphasize are (1) giving careful attention to actual good pediatric practice, (2) noting that there is no quantitative rule at present, or likely to be developed in the future, that will fit all drugs, (3) recognition of the fact that the child's dosage of some important drugs is much less different from the adult's than would be expected on the basis of a direct proportion to body weight, (4) acquisition of an attitude of humble enquiry in view of the fact that the basic quantitative data that might serve as a basis for dosage rules are, in the case of many drugs, not yet available in any systematic form.

Toward the end of the natural term of life, with basal caloric output falling, and with a decline in size of liver [62] and kidney,[68] caution in giving drugs is obviously necessary. But individual variability still plays a rôle, so that it may be necessary finally to use rather large doses of drugs in order to secure the desired effects, even in a little old lady. In short, after all this discussion, the only principle of dosage that survives is that the dose must be adjusted to the individual patient, and that nothing can or will supersede clinical experience, and careful study, combined with good judgment.

Conclusions

1. Laboratory observation has shown that the effective, usually lethal, doses of various drugs are usually less per kg. in the larger animals of a species than in the smaller. This is an over-simplification; a species may show either high resistance or high susceptibility at birth, with possible decrease for a few days or weeks, followed by increase.

2. On the basis of clinical observation the therapeutic dosage of atropine, the arsphenamines, bismuth, digitalis, mandelic acid, some mercurials, sulfanilamide and some other drugs, has been set at somewhat higher levels in proportion to weight for infants and children than for adults. On the other hand, dosage of morphine or strychnine, even in direct proportion to body weight, appears too great for safety of some individuals, and caution is in order until, at least, the susceptibility has been determined, especially in the case of an infant, child or aged person.

3. The greater tolerance of the young for some drugs may be due to various factors, possibly including proportionately larger average (1) surface area, (2) basal metabolic rate, (3) liver weight, (4) daily urinary volume.

4. The inevitable excretory and metabolic readjustments in the first few days or weeks of extrauterine life, as well as the decline in metabolic rate, reduction in size and possible pathological changes in liver and kidney after middle life (especially in old age) enjoin caution in the use of drugs during these periods.

Charts have been prepared to show the relative doses provided by various rules based on age, weight to various powers, surface area, and basal caloric output.

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ADENYLIC ACID IN HUMAN NUTRITION *

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From our studies of a large series of persons with mixed vitamin deficiency, we reported recently [1, 2, 3] that the diagnostic manifestations of pellagra, beriberi, riboflavin deficiency, vitamin A deficiency and vitamin B_6 deficiency respond to the administration of large amounts of synthetic nicotinic acid, thiamin hydrochloride, riboflavin, oleum percomorphum, and synthetic vitamin B_6 respectively. Each of these active chemical substances, in addition to its specific action for the relief of certain characteristic symptoms, promotes a general sense of well-being in these persons. Following the administration of crystalline vitamin supplements to their inadequate diets, the patients often became strong enough to work, with the result that a more adequate diet was subsequently bought and eaten. If the diet was not improved and these synthetic substances were added as supplements, better health followed, but many patients remained poorly nourished and continued to have symptoms. This suggests that even though these essential substances—nicotinic acid, thiamin hydrochloride, riboflavin, oleum percomorphum or carotene-in-oil, and vitamin B_6—are supplied, the diet is still deficient in another substance or substances. Since it has been shown in this clinic [4] and also by Sydenstricker, Geeslin, Templeton and Weaver [5] that riboflavin, in addition to its specific effect in the treatment of clinical riboflavin deficiency, is beneficial to certain pellagrins in relapse, and since so many of these "specific" deficiencies are clinically interrelated, it is possible that the same general biochemical system or systems may be disturbed. Adenylic acid is a constituent of the pyridine dinucleotides, coenzymes I and II, and is widely distributed in nature. It is intimately concerned with carbohydrate and protein metabolism. Therefore, we decided to investigate the properties of adenylic acid by administering it to normal persons and to persons with mixed deficiency disease.

Adenylic acid † was administered intravenously to eight normal persons, in doses of from 3 to 20 milligrams, dissolved in sterile physiological solution of sodium chloride. Within 15 to 30 seconds after the injection was begun, the subjects had an involuntary deep gasping inspiration, and complained of a burning and nervous "fluttering" sensation in the upper part of the abdomen and a feeling of fullness in the head. Oftentimes they

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stated that they were dizzy, and sweating of the forehead was observed in some of the subjects. Four of them had angor animi. All of the patients had transient flushing of the neck and face. The pupils became widely dilated; frequently there was blinking for several seconds. The arterial blood pressure fell slightly and the heart rate increased. All symptoms vanished within three to five minutes after they began, and there was no evidence of harmful effects. The possibility of impurities in the adenylic acid used is being investigated. The administration of a single dose of 200 milligrams of adenylic acid by mouth produced similar but less intense symptoms in about one-fourth of these persons, and some complained of headache. A similar oral dose, repeated every hour for five hours, did not increase the severity of these symptoms. Adenylic acid is only slightly soluble in water, but dissolves readily when incubated with normal human gastric juice. No toxic symptoms were observed when such gastric juice preparations were administered by mouth.

Group I. Two patients with pellagra in relapse were given 500 milligrams of nicotinic acid * daily as a supplement to their extremely deficient diet. This diet was unchanged during the period of observation. The immediate response to nicotinic acid was dramatic but after a period of six weeks, gradual relapse occurred. The daily dosage of nicotinic acid was doubled and another, but less dramatic remission was induced. The patients, however, did not remain symptom-free on this additional dosage. After diagnostic lesions of pellagra returned, 500 milligrams of adenylic acid were administered daily for three days, while the dosage of nicotinic acid remained constant. Dramatic relief of the symptoms occurred and the signs of pellagra once more disappeared in these two patients.

Group II. The second group consisted of seven patients with typical pellagrous plossitis and dermatitis. Each of these patients received 1000 milligrams of adenylic acid in divided doses for one day. Within 24 hours, the burning sensations in their tongues disappeared and they experienced a general increase in strength and sense of well-being. The glossitis and dermatitis, however, improved slowly and, in one case, not at all. When improvement occurred, it was gradual in contrast to the rather abrupt and dramatic relief of the mucous membrane lesions of pellagra following nicotinic acid therapy or the relief of the painful symptoms of beriberi following treatment with vitamin B_1.

Group III. This group of six patients, who had subsisted on grossly deficient diets for many years, had intense burning of the oral mucous membranes and, in some instances, of the skin. No diagnostic skin or mucous membrane lesions of pellagra were present. After failure to relieve these symptoms by means of placebos or nicotinic acid, 1000 milligrams of adenylic acid were administered orally, in divided doses of 100 milligrams

* In the presence of nicotinic acid amide or nicotinic acid, we have observed the in vitro synthesis of coenzymes I and II by defibrinated blood, but similar studies using pyrazine monocarboxylic acid gave no evidence of in vitro synthesis of these enzymes.

each, for one day. This was followed by immediate cessation of the symptoms. No return of burning was noted but this study was ended during the period when the diet was improved by summer crops.

These studies indicate that some of the symptoms of mixed vitamin deficiency are relieved by adenylic acid. This compound, in some cases, may act in a manner similar to riboflavin in increasing the effectiveness of nicotinic acid in pellagrins in relapse. This finding gives further evidence not only of the multiple and mixed nature of these dietary deficiency diseases in human beings but also suggests that they are the result of dysfunction of certain fundamentally related enzyme reactions. Because of the severe reactions produced by intravenous injections of all preparations of adenylic acid we have used, we do not recommend that this compound be administered to human beings until further studies are made. Investigation along these lines is in progress.

Summary and Conclusions

1. Pellagrins in relapse are benefited by treatment with nicotinic acid and adenylic acid.

2. Six patients with malnutrition, who had intense burning of the oral mucous membranes, but no diagnostic evidence of pellagra, were relieved following treatment with adenylic acid alone.

3. Since severe reactions were produced by the intravenous injection of three preparations of adenylic acid, we do not recommend that this compound be administered to human beings.

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VARIATION OF BLOOD PRESSURE WITH SKELETAL MUSCLE TENSION AND RELAXATION. II. THE HEART BEAT *

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IN previous studies [1, 2] systolic and diastolic pressure were measured in man, lying at rest, at intervals beginning about 15 minutes after reclining, while potentials were recorded (in microvolts within the frequency rate, 30–4000) from electrodes in one or more of the following groups: the flexor muscle in the right upper arm, the left quadriceps femoris muscles, the abdominal muscles, muscles in the region of the right eye. Apart from fall of pressure following soon after and attributable to change to the recumbent position, there were indications that the blood pressure variable is a function of skeletal muscular tension. Prolonged lying down did not in itself induce further lowering of pressure; in fact the pressure remained at about the same level or increased unless the subject relaxed. The data suggested that the ratio or decrement of pressure to decrement of muscular voltages, as recorded, was often greatest when the muscular voltages dwindled toward zero ($V_m \doteq 0$).

One factor in the chain of events leading to fall of blood pressure attendant upon skeletal muscular relaxation may be diminished rate and force of the heart beat. This possibility can be tested with the data at hand.

On many of the myograms made at the same time as the blood pressure tracings, small electrical records from the heart can be clearly distinguished, permitting the heart rate and the heart voltage there to be determined. More precisely expressed, the electrocardiogram indicates the potential differences in electrodes located about 4 to 6 c.m. apart in the arm or the thigh or the abdominal wall at a constant distance from the heart.

It must be admitted without reserve that the character of the QRS curves in the electrocardiograms of two individuals does not enable us to compare the force of beat in their hearts. Even in the same individual observed from day to day, the QRS curves admittedly would afford no basis for comparison concerning the force of the heart beat on different occasions, since the heart might shift in position in the chest and other essential conditions might vary also. These considerations should not obscure the possible value of the QRS curve in affording comparative data in the same individual concerning the force of his heart beat, *provided that essential conditions remain constant.*

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Einthoven and Hugenholtz,[3] answering many authors inclined to separate the mechanical and electrical phenomena of the heart beat, afforded their classic demonstration in 1918. Using a sensitive mechanical recording device, they found that in heart muscle poisoned with KCl solutions mechanograms could be secured so long as the electrocardiograms persisted. "All our experiments with poisoning, injury or removal of indispensable constituents have given us the same result, namely, a complete parallelism of the mechanical and electrical phenomena, always changing *pari passu*" is the statement of Einthoven in his Harvey Lecture (1924–25). Professor H. B. Williams has observed a patient evidently showing progressive muscular atrophy of the heart whose QRS curves declined accordingly (personal communication). He states his experience as follows:

"If you find in a new patient never before observed an electrocardiogram which looks very much like a normal one except that all is uniformly reduced, it may indicate general impairment of the myocardium and *it may not*. Some people have much lower voltage than average as a personal peculiarity. Such an EKG with a history of progressive narrowing of the field of cardiac response and a status praesens of shortness of breath on slight exertion with no valvular defects or anemia, I should regard as confirmatory of a tentative diagnosis of myocardial disease.

"If, however, you see a patient over a period of months and see the electrocardiogram progressively shrinking while maintaining its general form and with the shrinking of the EKG there is clinical evidence of diminishing effectiveness of the heart and valvular lesions are not present to complicate the situation, I regard it as proof positive of general myocardial disease."

The harmonious conclusions of Einthoven and Hugenholtz as well as Williams afford basis for the view that voltages in electrocardiograms are functions varying with the heart beat and that their magnitudes will enable us to compare force of heart beats in the same individual, provided that essential conditions will remain constant. We can assume that the presence of muscular contraction, however slight, will be denoted by action-potentials (Fulton,[4] Jacobson,[5] Davis and Davis[6]).

In the present studies, these conditions are met, because comparisons of voltages are made only in the same individual in a particular period of rest (60 to 90 minutes), while the electrodes remain in a constant position inserted in the tissues. It is an essential condition that the individual does not shift his position during these periods; even the limbs lie unmoved. Accordingly, in most or all instances, the position of the heart in the thoracic cavity may be assumed to be practically constant throughout. Therefore, it seems warranted to assume that in a particular individual during a specific experimental period, we can here follow the variations of force of the heart beat by measuring the heart voltages at corresponding instants.

The peak voltages measured in the present records differ from the QRS

of the electrocardiogram as commonly recorded with the string galvanometer in that the two electrodes are but 4 to 6 centimeters apart, both residing in the arm or in the abdominal wall. Under these conditions, I believe, the electrocardiogram shows much less variation during any single respiratory cycle than with the leads in their customary positions. This renders it unnecessary to make certain that the electrocardiograms to be compared occur always in the same phase of the cycle of respiration. A second difference results from the fact that the present electrocardiograms are recorded by means of amplifiers, transformer coupled. Amplification is required because the differences in potential marking the QRS curve, if recorded from electrodes only 4 to 6 centimeters distant from each other, as in one limb, must be measured in microvolts.

In 28 records it is readily possible to distinguish the electrocardiograms. The mean of several voltages was commonly taken as corresponding with each blood pressure tracing, since the latter was coincident with several heart beats. Accordingly we compare not one heart voltage with another, but the arithmetic mean of several heart voltages taken at the time of one pressure tracing with those taken at the time of another.

The results were not anticipated. There is in general a striking correspondence between fall in blood pressure and simultaneous decline in heart rate or in heart voltage or in both. In every instance (18 out of 28) where both systolic and diastolic pressure fall, there occurs a fall also in heart rate or in heart voltage or in both (10 out of 18). In the 18 instances mentioned, the fall both in systolic and in diastolic pressure averages about 9 mm. mercury, the decline in heart rate approximates 7 per minute and the diminution in heart microvoltage averages about 1.0 (table 1).

It seems reasonable to believe that a fall of 9 mm. blood pressure as an average is a significant figure; the more so, since this figure is added to the decline occurring upon lying down, so that the sum of the two falls constitutes an important fraction of the original pressure. (In order to eliminate subjective errors in taking blood pressure, the Tycos self-recording sphygmomanometer was used in these studies. The point of systolic pressure is sharply indicated on the charts made with this instrument; but there is question at times concerning the reading of the diastolic pressure. Accordingly we may believe that the figures for systolic pressure have a negligible error, but no such assumption is made regarding those for diastolic pressure. However, since all the readings were made by one person, we may assume that errors, if any, were in the same direction, and that the results for diastolic pressure are satisfactory at least for purposes of comparison.) The 28 records in question, as will be seen, include instances in which blood pressure did not fall. They also include instances in which action-potentials from the muscles in the arm or thigh or abdomen did not decrease; for in the present article, unlike the preceding one, we are not examining the possible correlation of changes in these potentials with changes in blood pressure.

A statistical analysis indicates clearly that the results are not due to

TABLE I

Changes in Heart Rate and Heart Voltage, Coincident with Changes in Blood Pressure

Subject	Age	Sex	Blood Pressure	Heart Rate	Heart Voltage
Ny.	20	M	−2/−5	−5	−0.8
Ad.	20	M	−5/+2	−3	−1.7
Ba.	22	M	−7/−13	0	−0.3
Et.	51	M	−7/+1	−3	−0.3
Et.	51	M	−12/0	−3	−0.3
Ro.	24	M	−18/−11	−12	−0.8
Ka.	30	M	−12/−18	−19	0
Lu.	27	M	+3/0	−4	0
Di.	37	M	−10/−5	0	−0.9
Ve.	35	M	−19/−25	−6	−0.3
Ve.	35	M	+1/−5	−2	0
Bn.	40	M	−1/−6	−12	+0.3
Bh.	35	M	−25/−2	−4	−1.4
Ma.	61	M	−7/−16	−5	−0.4
Ja.	24	M	+3/−2	−20	0
Adl.	20	M	+2/+9	−18	+0.3
Fl.	24	F	−2/−9	−4	−1.2
Ri.	18	F	−5/−6	−4	0
Od.	26	F	−5/−12	0	0
Mu.	23	F	−3/−1	−9	+0.3
Sh.	20	F	−4/−9	−12	−0.8
Ba.	22	F	−6/−1	+2	−0.4
Wi.	23	M	−2/0	0	−1.7
Eik.	24	M	−23/−10	−9	−5.7
Ga.	23	M	−11/−8	−15	−1.4
Bo.	28	M	0/−3	−9	−0.3
Th.	?	F	0/−1	0	+0.1
Ed.	20	M	−9/−9	−6	−1.4

chance variation. The following summary has seemed most simple and is modified on suggestions for which I am indebted to Professor Walter Bartky. In any one of the 28 records considered, coincident changes respectively in systolic pressure, diastolic pressure, heart rate and heart voltage are possible in 16 varieties. As indicated in table 2, let W_1 represent

TABLE II

Statistical Analysis of Table 1;
Possible Coincident Changes in 4 Variables
Systolic Pressure, Diastolic Pressure, Heart Rate, Heart Voltage

W_1	W_2	W_3	W_4	W_5
− − − −	− − + −	+ − − −	+ + − −	+ + + +
	− − − +	− + − −	+ − + −	
		+ + + −	+ − − +	
		+ + − +	− + + −	
		+ − + +	− + − +	
		− + + +	− − + +	

Scores[1]

	Random	Actual
W_1	1.75	13.50
W_2	3.50	6.00
W_3	10.50	6.00
W_4	10.50	2.50
W_5	1.75	0.0

[1] In scoring, it is necessary to consider zero as midway between minus and plus and to credit the value, 1/2 to W_1 or to W_2 or to W_3 as the case may deserve.

— — — —, W_2 represent — — + — and — — — +, while W_3, W_4 and W_5 represent the other groups of combinations there shown. We are particularly interested in W_1 and W_2 but most of all in W_1, the instance in which there is decrease in systolic and in diastolic pressure accompanied by decrease also in heart rate and heart voltage. The chance score for W_1 would be $\frac{1}{16}$ of $28 = 1.75$. Actually we find that W_1 occurred 13.50 times. Obviously this result differs very greatly from the purely random score stated above; so much so that it seems superfluous to determine the probability figure. The same can be said regarding the actual score of $W_1 + W_2 = 19.50$, compared with the random score of $W_1 + W_2 = 5.25$.

In the score of 28 instances considered, decreased systolic plus diastolic pressure occurs in 20 instances. Most of these 20 instances are accompanied by decrease both in heart rate and in heart voltage (13.5 out of 20); all of these 20 instances (except one half of one, as scored) are accompanied by decrease at least in heart rate or in heart voltage.

Obviously, decline in the force of beat (represented by voltage, in the present instances) or decrease in the rate, while the strength remains approximately the same, indicates relaxation in the cardiac musculature; more precisely stated, indicates less effective or fewer beats during a given period of time.

Is the recumbency in itself responsible for the lowering of blood pressure and also of the diminished heart rate and heart voltage? This question was answered negatively in the preceding article; for during about 15 minutes after the change from sitting or standing, there occurred an initial fall, but no further decline in pressure upon prolonged recumbency, unless relaxation increased during the period. Accordingly we infer that cardiac relaxation tends to accompany relaxation in the skeletal musculature and that this should be taken into account in explaining the blood pressure fall which tends to occur in an individual lying down, if and when contractions in his skeletal muscles diminish.*

In two subjects (Th and Ve, figures 3 and 5, loc. cit.) blood pressure shows no significant fall. Do the heart rate and heart voltage decline in these instances as they generally do in those where the fall in pressure averages about 9 mm.? In Th, taking the initial pressure as $^{121}\!/_{76}$ mm. of mercury and the pressure after the attempt to relax (which met with failure) as $^{121}\!/_{75}$, the pressure remains practically the same. So also does the pulse rate—100 both times. The microvoltage from the heart remains practically constant, namely 7.4 and 7.5 at the two times. In Ve, while relaxing, the pressure is $^{101}\!/_{59}$ initially, changing to $^{102}\!/_{54}$ after 45 minutes further relaxation. This change is so slight as to lie within the probable limits of error in taking and reading the pressure, so that it may be regarded as practically an equality. Correspondingly, the heart rate varies insignificantly, namely,

* In the 20 instances considered above, relaxation in the skeletal musculature is inferred rather than demonstrated to be concomitant with the cardiac relaxation. Checking on this correlation will be considered in a later article.

from 62 to 60, while the heart microvoltage is initially 2.0 and does not change from this value. In short, the heart rate and heart voltage do not decline significantly in these two instances where blood pressure also does not decline during the period of recumbency. Accordingly these data for heart rate and heart voltage permit us to believe that under the present conditions variation or constancy in blood pressure depends (among other factors) to a noteworthy extent on corresponding variation or constancy in the force (voltage) and rate of the heart beat.

Comment

Assuming that blood pressure tends to vary with skeletal muscle tension (en masse or perhaps preponderantly with tension in certain groups, such as the abdominal muscles), there evidently are various other possible physiological mechanisms. One would be relaxation of muscle fibers in the arterioles and in the muscular arteries—a diminution of vascular tonus. This would be analogous to relaxation in other visceral muscle tissue, notably in the lowermost portion of the esophagus, which, as I have shown, can occur upon relaxation of the skeletal musculature. Our present knowledge is insufficient to permit us to say by what channels this relaxation of arterial musculature might be effected, but there are four plausible hypotheses:

1. The contracting fibers stimulate sensory end-organs in the muscle spindles, arousing afferent impulses which proceed to excite nerve-centers in the cord or perhaps even in the brain, which exert pressor influences by way of the sympathetic nervous system. Relaxation reduces this stimulation at the source and so effects a reduction of pressure.

2. Possibly skeletal muscle contraction, even in minimal degree, is accompanied by secretion of a pressor substance by some gland such as the suprarenal, or by some other organ, or possibly,

3. The pressor substance comes during contraction from the neuromuscular junction (acetylcholine) or from the muscle tissue itself, then passing to the blood stream.

4. Skeletal muscle contraction in intact man occurs only along with activities in divers portions of the nervous system. At least a portion of the somatic motor system participates whenever we perform an involuntary as well as voluntary act. Commonly what takes place is brain-cord-efferent nerve-muscle-afferent nerve-cord-brain-cord etc. action. In this recurrent chain of acting tissues, we are accustomed to assume that the brain is the first to act, but it is by no means certain that this traditional view is entirely justified. This leads to the consideration that the influence on blood pressure may be initiated in one or more of the various regions which take part in the total act of voluntary or involuntary contraction as above defined. Perhaps one region of such initiation is in the cortex. Evidence has recently been furnished by Hoff and Green [7] that nerve elements controlling blood pressure exist in the cortex adjacent to somatic motor centers.

Summary and Conclusions

1. If, in man, beginning about 15 minutes after lying down, there occurs sufficient decline in skeletal muscular action-potentials, a fall in systolic and diastolic pressure characteristically takes place also (loc. cit.). Under these conditions, or if, at least, no marked increase in muscular action-potentials occurs, a decrease in cardiac voltage and rate, or in one of them, attends the fall in pressure. The data are insufficient to test whether there is parallelism between the curves of action-potentials from skeletal muscles and from cardiac muscles.

2. Fall in blood pressure upon skeletal muscle relaxation presumably depends upon relaxation in muscle fibers of the circulatory system, notably in the arterioles, in the muscular arteries and perhaps in the heart, but possibly, also, relaxation in the muscle beds containing capillaries is a factor. Precisely what physiological channels are involved has not been determined, but possibilities are discussed. Measurement of the heart rate and heart voltage approximately simultaneously with the blood pressure reading affords data which indicate that one factor presumably effective in the observed fall in pressure during protracted muscular relaxation is diminished force and rate of the heart beat. In some instances where relaxation remained constant and the blood pressure did not change markedly, the heart rate and voltage also remained practically unaltered.

3. The results suggest that, upon lying down, even individuals with "normal" blood pressure commonly show heart action a little faster and more forceful than would occur if they were more relaxed in their skeletal musculature. They suggest also that in "essential" hypertension the heart muscle may be unnecessarily "tense," showing, even when at rest, a somewhat excessive rate and voltage, as compared with lower values attained if the individual is considerably more relaxed.

4. The findings furnish some additional foundation for the view that high blood pressure in "essential" hypertension can result in part from habitual activity involving hypertensive states in the skeletal musculature.

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LIMITATIONS OF RENAL FUNCTION DETERMINATION *

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THE improvements in biochemical methods have given great impetus to the use of the clinical laboratory by physicians. Procedures which were originally interesting laboratory confirmations of diagnostic impressions of an alert physician at the patient's bedside, later became routine studies on hospital patients. The precepts of pioneers in the use of laboratory tests have led to the increasing application of such procedures in accepted medical practice. It seems logical to utilize all possible aids in obscure and chronic disease, particularly for their benefit in preventive medicine.

As the biochemist strives to devise methods for the measuring of physiologic function in various organs of the body, a disconcerting diversification in the abilities of any organ becomes apparent. The as yet innumerable functions of the liver and kidney are becoming more evident. Diversified physiologic activities require a corresponding variety of properly devised test methods. It is evident that the clinician must decide what specific function is to be measured, and the clinical pathologist must have a method of suitable specificity if reliance is to be placed on laboratory reports indicting the functioning ability of any organ.

The laboratory contribution to knowledge of the state of the kidneys comes, aside from the examination of the urine and blood, in the study of the following: 1. Ability of the kidneys to concentrate and dilute the urine. 2. Ability of the kidneys to eliminate foreign substances introduced into the body. 3. Ability of the kidneys to eliminate easily measured normal constituents of the blood (clearance tests).

There is no unanimity of opinion as to the best renal function test in present clinical usage.[1-16] The urea clearance procedure has had widespread application following the careful and extensive study of its use by Van Syke and collaborators [1, 17-20] at the Rockefeller Institute. Van Slyke finds the urea clearance fairly immune to unpredictable extra-renal influences, especially disturbances in water metabolism. He also finds that a normal clearance does not necessarily prove the absence of renal disease, but states that he does not consider the performance of a multiplicity of tests necessary.[18] Alving and Van Slyke [1] warn that normal clearances are encountered in the presence of obvious renal abnormality in the following conditions: 1. Mild acute nephritis. 2. Recovery stage of acute nephritis. 3. Some cases of nephrosis. In recovery from acute nephritis a low specific gravity persists long after the clearance returns to normal.[1, 6] It was further found that in

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cases of essential hypertension and nephrosclerosis showing normal urea clearance the concentration tests are likely to be normal, i.e., the clearance and concentration tests show the same relative behavior.[1]

Dodds and Robertson [21] think that the urea clearance is perhaps the most valuable of all renal function tests, while in the hands of Chapman and Halsted [2] the fractional phenol red test is as informative as the urea clearance. Leiter [6] and McDonald [22] consider the urea clearance the most reliable single test in their experience with renal function measurements. Freyberg [4] finds, on good evidence, that the concentration test of Lashmet and Newburgh [12, 23] is the most sensitive test of renal efficiency, often demonstrating impairment of function when other tests fail to do so. Kestel [10] likes the concentration tests best of all. Thomas [8] prefers a quantitative metabolic study such as the Mosenthal test day meal.

In an attempt to clarify the issue McDonald [5] points out that in one instance the difficulty in excretion pertains to the nitrogenous metabolites, whereas in another the difficulty is in excretion of water and salts. He concludes, " it is hardly conceivable that any single ideal test for renal function, especially in the diseased kidney, can ever be attained." He looks upon an adequate concentration test as probably the most sensitive indicator of damaged renal function. Ellis and Weiss [7] stress the fact that alterations in the formation of urine may occur from disturbances of either the filtration or reabsorption activities of the kidney. They use the creatinine clearance of Rehberg as a " direct indication of the amount of glomerular filtration " and stress that, under conditions of maximal excretion, the urea clearance also gives a relative index of the degree of filtration since with urinary excretions exceeding two cubic centimeters per minute the percentage of back diffusion of urea through the tubules is nearly constant. For tubular function Ellis and Weiss [7] consider the concentration test the best measure of the ability of the kidney to reabsorb water and, hence, of tubular activity. In conclusion, the authors emphasize the increasingly obvious fact that " no single technical procedure is adequate to test thoroughly the function of the kidney . . . these laboratory methods are of value only in supplementing clinical observation. They supply worthwhile information only when conducted with care under controlled conditions and the results obtained require careful interpretation." Leiter [6] summarizes the factors in such a careful interpretation as follows: " It is evident that the information acquired in this manner is a resultant of several factors, namely, the degree of parenchymal integrity of the kidney, the volume of blood flowing through the organ during the period of the test, the activity of compensatory physiologic or anatomic changes, and the presence or absence of various extrarenal conditions. The net result is a quantitative value for kidney function at the moment. Nothing is learned which is responsible for the quantitative change. Nor does one know from renal function testing alone whether the change has occurred in the remote or recent past, whether it is still active, or whether it will subside in the near or distant future." Harding and Urquhart,[24] Van Slyke,[19]

and Bowen [11] have stressed the influence of factors other than functional activity of kidney units on the kidney function tests. McCance [25] has demonstrated that disturbances in plasma electrolytes, for example low chloride values, may result in high blood urea values with temporary impairment in renal function, in the absence of nephritis in the clinical sense.

The present investigation concerns the application of four commonly used clinical methods, namely, the early morning urine specific gravity after a 12 hour fast, the excretion of phenol red, the urea clearance, and a combined dilution and concentration test similar to those used by Volhard, Lundsgaard, Rosenberg and others.[1] Purposely, the usual clinical laboratory equipment was selected in place of refinements in apparatus which are not commonly used. This observance, together with the fact that we have no new or favorite renal function test to present, will, it is hoped, render the results fairly applicable to the average hospital laboratory.

The use of phenol red in the study of kidney function was introduced by Rowntree and Geraghty.[26] As Chapman and Halsted,[2] Shaw and McKenzie [27] found the elimination of phenol red in the first 15 minutes to be a more reliable indicator of renal function than other periods in fractional dye excretion studies, such a procedure was adopted for the present study. The history of the use of urea in measuring renal function has been described elsewhere.[18] Van Slyke accepts as normal anything below 23 mg. urea nitrogen per 100 cubic centimeters of blood. Only after the urea clearance is 20 per cent or less of normal does an elevated blood urea commonly occur.

The morning specific gravity observations were made on 77 individuals for controls. The other methods, described below, were applied to 100 patients showing no evidence of disease, for the purpose of establishing controls. A separate group of 290 patients were selected for study. Each patient in this group presented a history, physical findings, or urinary sediment indicating renal disease. In other words, in each patient of the experimental group there was definite reason to suspect some degree of impaired renal function before the function tests were applied. In the beginning an attempt was made to use the method of Lashmet and Newburgh [12,23] to obtain the maximum specific gravity. From the ward patients we heard undue complaining of thirst, frequent refusals to coöperate. Occasionally the patients obtained water surreptitiously. For such reasons the attempt to determine the *maximum* urine concentration routinely was abandoned. An indication of the concentrating ability was obtained (*a*) by noting the specific gravity of urine after withholding fluids for 12 hours, and (*b*) by noting the maximum change in specific gravity after taking a large volume of water (i.e., the lowest reading in the urine specific gravity following the ingestion of 1500 cubic centimeters of water in the morning subtracted from the highest reading in the afternoon). From our preliminary experience with the procedure of Lashmet and Newburgh [12, 23] we have reason to believe that it is superior to all methods for estimating maximum concentrating ability. Its drawback lay in the lack of coöperation from the

average ward patient with the hospital attendants in the effort to obtain adequate dehydration.

Methods

The methods employed were as follows: The patient received a standard "house diet" in the hospital for 48 hours prior to the tests. No fluids were allowed from seven o'clock in the evening until seven o'clock on the morning of the dilution and concentration tests. No breakfast was given. At seven o'clock in the morning a specimen was taken for routine urinalysis. Between seven and eight in the morning the patient drank 1500 cubic centimeters of tap water. Urine was collected at the following hours: 7:30, 8:00, 8:30, 9:00, 9:30, 10:00, 10:30, 11:00, 11:30, 12:00, 1:00, and 2:00. A dry lunch (containing nothing which could be poured) was allowed at 11:30 in the morning during the test. The volume was measured and the specific gravity of the various specimens was determined by means of a standardized clinical urinometer. A notation was made of the four hour volume excreted from 7:00 until 11:00 in the morning. The urine collected between 9:00 and 10:00 and between 10:00 and 11:00 o'clock was taken for determinations of the urine urea by the method of Koch.[28] Blood for urea estimation by the method of Koch was taken at 10:00 o'clock. From this the urea clearance was calculated by the formula of Van Slyke [17, 18] for maximum urea clearance. The patient remained in bed during the procedure outlined above. On a separate day (usually the day before or immediately after the above) 6 mg. of phenol red were given intravenously 30 minutes after the patient had taken 16 ounces of water. Urine was collected after 15 minutes and two hours. Each patient had a recorded history and physical examination with notes on clinical observations which might affect the measured function. Tabulations made from these charts include the following information: Name; age; sex; urinalysis, including microscopic findings on centrifuged specimens; phenol red excretion for 15 minutes and two hours with the volumes excreted; the largest and smallest volume and the highest, lowest, and early morning specific gravity readings of the urine (including the hour of each) after 1500 cubic centimeters of fluid; the four hour volume during the dilution test; the urea clearance in terms of percentage of normal; the diagnosis; blood pressure; and, in a miscellaneous column, facts in the history, physical examination, or laboratory reports of significance in each patient. Corrections for albumin in the urine were made according to Lashmet and Newburgh [23] for the specific gravity readings of urine ($0.003 \times$ per cent of protein).

After plotting the results of tests on the control series one finds notable left skewing in the frequency distribution diagram for urea clearance, phenol red excretion and Volhard type concentration tests (charts 2, 3, and 4). The figures for early morning specific gravity are fairly symmetrically distributed and give a mean of 1.026 and a standard deviation of ± 0.003 (chart 1).

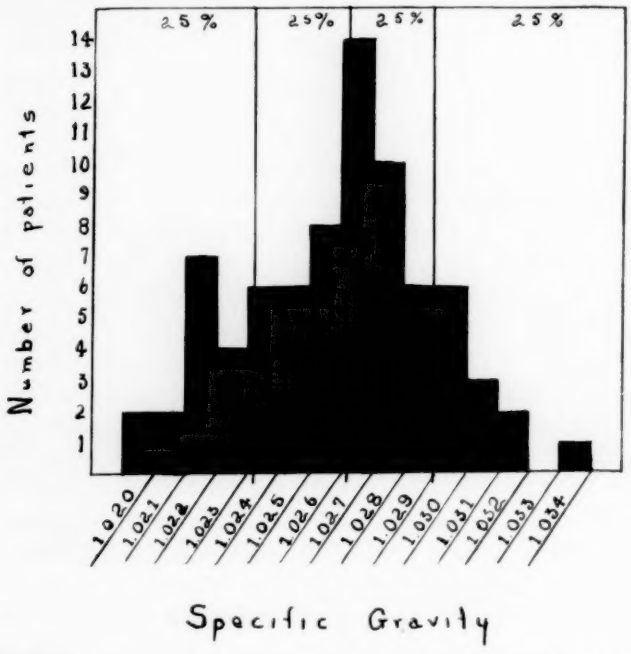

CHART 1. Distribution of morning specific gravities after 12 hour fast in normal adults. Mean 1.026, standard deviation 0.003.

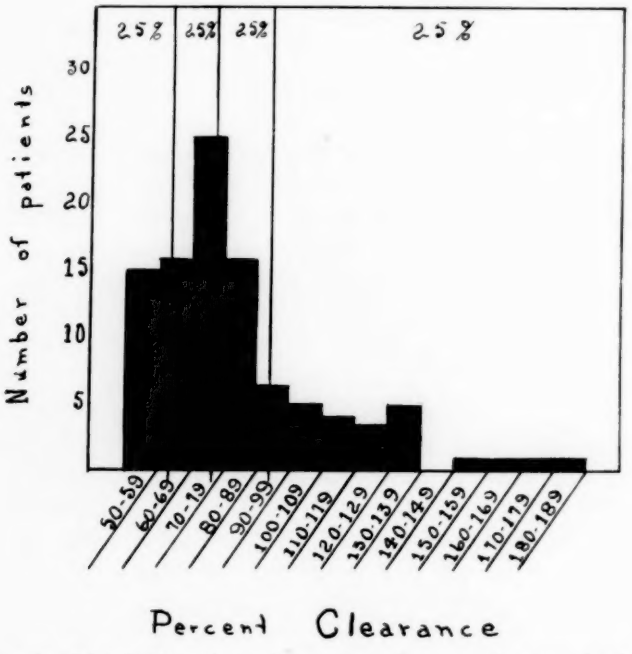

CHART 2. Distribution of maximum urea clearances in normal adults.

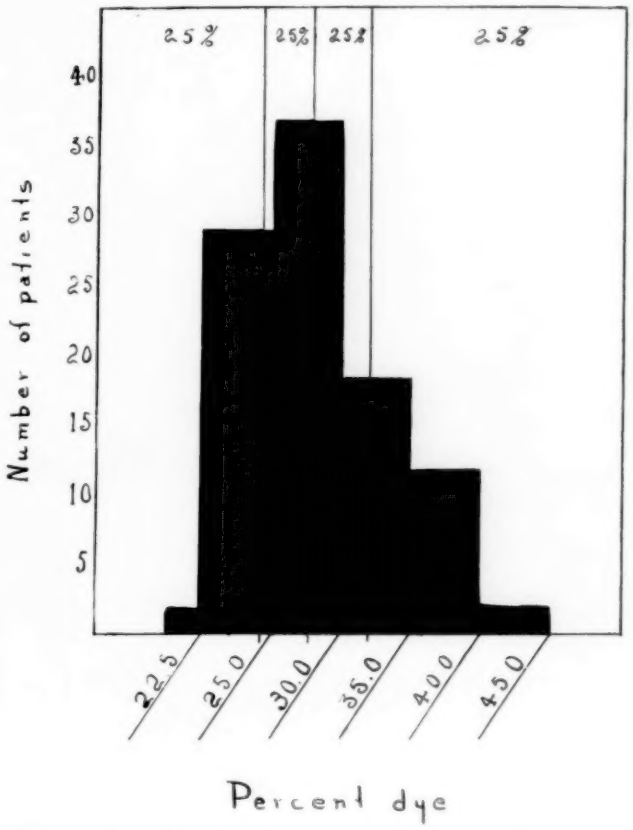

CHART 3. Distribution of phenol red excretions 15 minutes after intravenous injection of the dye in normal adults.

For purposes of interpretation of results in the diseased group of patients, urea clearance readings below 50 per cent (assuming 75 cubic centimeters of blood cleared per minute for maximum clearance in the normal) were regarded as showing evidence of renal disability. Excretion of less than 25 per cent phenol red in 15 minutes, a change in specific gravity during the Volhard type concentration test of less than 0.010, and a morning specific gravity of less than 1.020 was taken as evidence of inadequate function for the particular test.

The clinical diagnoses are shown in table 1. An effort was made to separate those patients with the suspected etiology of renal arteriosclerosis without hypertension from the group showing nephrosclerosis with hypertension. Hypertension was arbitrarily taken as a systolic pressure reading above 150 millimeters *and* diastolic reading above 92 in a reclining patient. For each group the number of instances in which the phenol red excretion, the concentration tests, and the urea clearance were found to be impaired is given. It is found from table 1 that the 15 minute phenol red excretion is more apt

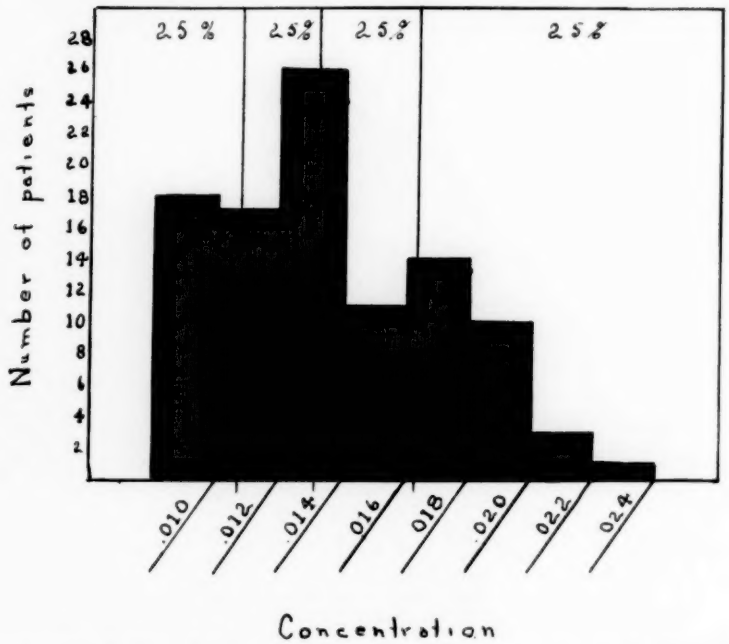

CHART 4. Distribution of degrees of variation in specific gravity obtained by subtracting lowest morning reading from highest afternoon reading. Volhard-type concentration test in normal adults.

TABLE I

The Incidence of Impaired Function Tests in Relation to the Clinical Diagnoses

Diagnostic Class	Number Patients	Impaired PSP Excretion		Impaired Concentration		Impaired Urea Clearance	
		Number	%	Number	%	Number	%
Arteriosclerosis (without hypertension)	70	62	89	48	69	36	51
Arteriosclerosis (with hypertension, benign and malignant)	86	68	79	60	70	62	72
Hemorrhagic Bright's disease:							
(*a*) acute	16	12	75	4	25	6	38
(*b*) subacute	16	12	75	4	25	10	62
(*c*) chronic	26	24	92	22	85	24	92
Degenerative and toxic Bright's disease (including pyelonephritis, toxemias of pregnancy)	52	46	88	28	54	30	58
Congenital polycystic kidneys	2	2	100	2	100	2	100
Unclassified	22	16	73	10	45	16	73

to show evidence of disease in patients with arteriosclerosis and without hypertension than is the specific gravity or the urea clearance. This is likewise true for the patients with degenerative Bright's disease from various causes.

In only 94 of the group of 290 patients in whom renal disease was suspected, did all tests show evidence of impairment. Inasmuch as the results of the dilution test paralleled those of the concentrations in all but three instances, the former is omitted from separate consideration. Table 2 groups those patients, aside from the 94 having diminished function in all tests, with disease manifest by one or two of the procedures employed.

TABLE II

Impaired Renal Function Indicated by but Two of the Test Methods

	Number of Patients
Phenol red plus urea clearance	56
Phenol red plus dilution and concentration	54
Dilution and concentration plus urea clearance	18

Impaired Renal Function Indicated by but One of the Test Methods

	Number of Patients
Phenol red alone	32
Urea clearance alone	30
Dilution and concentration alone	6

COMMENT

Laboratory procedures, to be helpful to the clinician, must have their advantages and limitations defined. The relative dependability or lack of specificity should be recognized by the successful clinical pathologist as well as the clinician. Otherwise, harmful misdirection in planning the patient's existence results not infrequently. Astuteness in interpretation of all evidence pertaining to a patient's illness is rendered more necessary than ever by the increasing multiplicity of laboratory aids. In the group of patients studied clinically and reported here, it is noted that only in the instances of advanced renal disease did all function tests agree. Each member of the group of 94 furnished sufficient evidence in the anamnesis, physical examination, and the urine sediment to assure a physician of the presence of moderately advanced disease without the confirmation of function tests. The group represents patients so advanced in their disease that little effective medical protection can be given.

It is highly important that early signs of disease be recognized. This applies to subacute or chronic hemorrhagic Bright's disease, the toxic and arteriosclerotic types as well. It is to the interest of the patient that renal tests indicate changes in the maximum functioning ability of that organ sufficiently early to allow steps to be taken to give some effective degree of

rest and protection before the stage of renal failure has been reached. The tests employed do not appear to meet this requirement satisfactorily. Don,[3] after comparing the function tests in 64 patients having impaired renal excretion observed that, "In making comparison one was struck by the fact that while on one occasion one test would seem to be the most sensitive, in another case it would seem to be the least sensitive. . . . The phenolsulphonthalein is not regarded as a very sensitive test, yet in many cases, chiefly those with a high blood pressure, I found it to be apparently a delicate test and low results were obtained more often than I expected. It was still more surprising to find that it sometimes showed an apparent loss of renal function before the urea clearance test. . . . To conclude, the failure of the tests to agree closely with one another suggests either that they are not completely reliable or that different renal functions are being measured."

Under disadvantages described for the urea clearance are: 1. Accurate collection of urine for a given period is necessary.[6] 2. Exacting procedures are needed for the careful quantitative determinations of blood and urine urea.[6] 3. Penington [29] stated that the rate of urea excretion is increased by the administration of milk, caffeine and glutamic acid by mouth, decreased by exercise, pituitrin and large amounts of adrenalin. On the other hand, Page [30] found that diuretics, salyrgan, caffeine and diuretin do not alter the ability of the kidney to excrete urea. 4. Van Slyke [19] observed that extra-renal factors as changes in blood supply resulting from shock, reflex anuria after surgery, cardiac decompensation, interfere with the clearance. Obviously, similar objections may be made to other tests of renal function.

Concentration tests are commonly invalidated because of extra-renal influences of endocrine, nervous or metabolic origin.[1, 6, 7] Diuresis at the time of the test in an edematous patient makes impossible the carrying out of sufficient dehydration to obtain a sufficiently high specific gravity of the urine. When the diet of the patient has been low in protein and salt there may not be sufficient excretion of waste products in even small volumes of urine to grant a high specific gravity that should occur with normal renal function. A low specific gravity may be found in anemias, pyelitis, prostatic hypertrophy, urethral strictures, paralysis of the bladder. Low specific gravity is a regular finding in diabetes insipidus.

Disadvantages in the use of the phenol red test have likewise been described. Leiter [6] finds that cardiac failure has an unusually depressing effect on the elimination of phenol red by otherwise normal kidneys. A certain amount of dye is held by blood proteins. Increased absorption might well prevent an adequate test. Thomas [8] speaks of the uncertain fate of part of the phenol red in the body tissues, and finds that pregnancy interferes with its excretion. Freyberg, Gillard and Ganesbauer [9] find the 15 minute phenol red excretion unreliable in the last trimester of pregnancy. As is common knowledge, urinary pigments dilute the red color and give rise to uncertain matching of the dye. Collins [31] found a yellow color filter useful in the matching of phenol red with the standard solution. Of various sug-

gested procedures for removing bile pigments in urine [32] the use of aluminum hydroxide was found to be the most satisfactory in our laboratory. This is troublesome, and at times seems to give a false low reading for the dye present.

At times it was observed that even after adequate preparation of the patient the volume of urine excreted was low, or the patient could not void at the required minute. For the 15 minute determination of dye excretion it is essential that the patient void completely or be catheterized at the proper time. This means occasional repetition of the test. Twice the presence of hemolyzed blood in the voided specimen invalidated the reading. At other times the color of the diluted and alkalinized urine was of such a bizarre hue that matching was impossible. No explanation has been found for the latter behavior.

The dilution and concentration tests of the Volhard type are of no service in the patient who vomits easily from any cause. The test is nullified occasionally by the presence of duodenal obstruction or other gastrointestinal disease interfering with rapid absorption. It is found useless, of course, in the presence of edema, hepatic cirrhosis, hepatitis, or ascites.

A practical defect in the urea clearance estimation is discovered in occasional errors in the time of the collections of the urine by hospital attendants. Coöperation of the nursing service as well as that of the patient is required in getting the exact time of the voidings and insuring complete emptying of the bladder. In a few instances inordinately high urea clearances were obtained—200 per cent or more than normal. These are inexplicable in spite of careful checking of the calculations and the consistent use of duplicate determinations. In such patients a normal clearance figure may be found the following day. One wonders if such a peculiar clearance might not occur infrequently at a lower range and give a false normal reading in diseased kidneys.

At best it seems that the present laboratory estimations of renal function fall short of the clinical requirements. It is hoped that future efforts in function testing may be directed toward measurement of the specific separate functions of the kidney, keeping in view the anatomic basis for renal disease. The functional adequacy of the blood supply, the glomeruli, and the tubules may ultimately lend themselves to separate measurement. Progress is being made toward this ideal. The difficulties encountered in the approach to adequate and safe methods which will measure accurately for the clinician the separate functions of the kidney are clearly indicated in the review of knowledge of renal tubular excretion by Shannon.[33]

Conclusions

It is obvious that no one test was adequate in the clinical study of these patients. The 15 minute excretion of phenol red gave expected results more often than any other measure employed. From this experience it appears that phenol red cannot be displaced by any available procedure in convenience

and accuracy for clinical use. When combined with the urea clearance determination, laboratory confirmation of renal disease was obtained in all but six of a group of 290 patients presenting good clinical or urinary sediment signs of renal disease.

Note: The authors are indebted to the nursing service of Davis Memorial Hospital for faithful coöperation, to Mr. C. L. Corder for loyal assistance in the required urinalyses.

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CLINICAL STUDIES IN RENAL DISEASE. III. ACIDOSIS IN CHRONIC GLOMERULONEPHRITIS *

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UREMIA is a toxic state associated with an abnormal accumulation of nitrogen bodies in the blood. It is characterized clinically by anorexia, nausea, vomiting, weakness, restlessness, headache, drowsiness or coma. The exact nature of the toxemia of uremia is not known, although such substances as urea, uric acid, creatinine, phosphates, sulphates are present in the blood in excessive amounts. It was Bright himself who first designated as uremia the group of symptoms characteristic of renal failure, because he thought these symptoms were due to a retention of urea in the blood. Bright regarded urea as a highly toxic substance but it is now generally acknowledged that he was mistaken, for in Bright's disease there may be a very high concentration of urea in the blood without symptoms of toxemia. It is to be stressed, however, that uremia is always associated with marked urea retention in the blood as well as in the tissues and the demonstration of this retention establishes the diagnosis.

The toxemia characteristic of the uremia resulting from Bright's disease is dependent upon many factors. Sepsis, malnutrition, dehydration, oliguria, cardiovascular insufficiency, respiratory complications and anemia, singly or collectively are obviously important. The presence of any one of these factors will not only aggravate the existing renal insufficiency but may lead to a fatal ending regardless of the degree of actual renal damage.

Knowledge of the exact mechanism of the symptoms of uremia is incomplete and the physiological cause of death is obscure. An important factor is acidosis which was first described in Bright's disease by Von Jaksch [1] in 1888 and subsequently confirmed by recent studies. This acidosis in nephritis has been discussed at length by Peters and Van Slyke [2] who report that in fatal cases of nephritis, extreme acidosis comparable to that seen in diabetes mellitus may exist and stress that in terminal nephritis acidosis "may attain a severity great enough in itself to menace life." The clinical importance of this fact has not been emphasized generally and with this in view the results of a study of the symptoms and the CO_2 combining power in a group of 50 cases of chronic nephritis are presented in this paper.

A diagnosis of chronic nephritis was made by the findings of hypertension, anemia, urea nitrogen of 50 mg. or more, a low fixed specific gravity, and red blood cells and casts in the urinary sediment. In all of our patients the nephritis had undoubtedly existed for many years. Symptoms of toxemia had been present for only a short time because the symptoms leading to admission to the hospital had existed for a period of less than 30 days.

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Acidosis (a CO_2 combining power of 40 vol. per cent or less) was found in 36 patients (table 1). The symptoms of uremia were found to be not unlike those of acidosis of any cause (table 3). Acidosis, once developed, manifests the same symptoms whatever the factor responsible for its inception. It is of primary importance in chronic nephritis with uremia.

TABLE I
Blood Chemistry
Mg. per 100 c.c.

No.	Age	B.P.	CO_2 Vol. %	Cr.	Ca.	PO_4	Urea N	Days in Hosp.	S.S.*	R.†
1.	33	200/130	35.6	4.5	9.6	5.8	160	24	m.	I.
2.	49	190/110	12.6	9.0	—	—	160	34	S.	D.
3.	26	260/160	23.0	9.2	7.5	17.2	140	6	S.	D.
4.	59	200/140	24.0	12.0	9.2	9.4	250	11	S.	D.
5.	65	180/85	32.4	8.25	—	—	91	17	S.	I.
6.	31	195/110	35.0	4.0	9.5	4.4	110	21	S.	D.
7.	47	210/105	33.4	12.0	5.9	16.4	176	9	M.	I.
8.	60	110/60	29.6	5.0	—	—	115	4	S.	D.
9.	24	225/155	35.3	12.0	10.0	9.4	150	18	M.	D.
10.	34	212/130	13.7	4.0	6.5	6.5	60	5	S.	D.
11.	64	110/70	39.3	1.58	—	—	60	10	M.	I.
12.	52	168/90	13.6	8.0	7.0	12.4	130	28	S.	I.
13.	76	128/70	52.2	2.5	—	—	75	18	m.	I.
14.	60	220/100	60.7	2.67	—	—	80	10	m.	I.
15.	33	150/80	41.9	2.5	7.9	2.2	55	8	m.	I.
16.	28	210/140	23.6	8.4	6.8	23.6	100	12	S.	I.
17.	60	100/94	37.5	2.36	—	—	60	17	S.	I.
18.	51	160/90	37.6	3.7	7.0	8.0	73	12	m.	I.
19.	39	140/80	10.3	10.0	5.8	14.0	200	4	S.	D.
20.	24	210/170	26.5	8.0	6.8	11.6	125	14	S.	D.
21.	34	142/78	14.5	9.0	9.6	12.0	176	5	S.	D.
22.	33	54/0	41.0	1.67	8.7	7.2	74	7	m.	I.
23.	49	180/100	42.8	10.0	8.6	11.4	136	9	m.	I.
24.	60	60/60	47.0	6.0	—	—	140	10	m.	I.
25.	80	172/80	52.6	2.5	—	—	80	26	m.	I.
26.	47	140/68	33.8	12.0	—	—	220	12	S.	D.
27.	61	190/100	38.3	3.0	—	—	85	34	S.	I.
28.	30	270/175	32.0	2.0	12.2	6.4	55	42	m.	I.
29.	25	245/155	26.8	8.0	9.5	8.0	100	3	S.	D.
30.	54	195/100	23.0	8.5	5.5	18.0	140	2	S.	D.
31.	32	250/160	27.0	12.0	8.6	18.0	375	7	S.	D.
32.	34	160/90	53.0	4.2	—	5.6	150	26	m.	I.
33.	51	200/98	43.0	6.6	10.0	5.3	94	31	M.	I.
34.	29	200/160	45.0	12.0	10.6	16.5	220	23	M.	I.
35.	46	220/120	29.0	8.6	9.8	9.2	190	36	S.	I.
36.	70	230/100	46.0	2.0	7.4	4.5	192	7	M.	I.
37.	46	145/95	26.0	7.5	6.0	8.4	150	18	S.	D.
38.	67	130/80	48.6	2.5	—	—	60	12	m.	I.
39.	54	220/140	37.0	6.0	10.0	6.0	100	22	M.	I.
40.	60	225/110	38.0	3.7	9.5	4.4	85	7	M.	D.
41.	31	118/65	28.0	3.3	12.0	14.8	75	16	S.	I.
42.	28	120/70	42.0	20.0	6.4	17.6	340	25	M.	I.
43.	65	190/120	52.0	2.2	9.2	4.2	50	12	M.	I.
44.	47	250/180	17.0	10.0	7.0	16.8	200	5	S.	D.
45.	47	140/72	9.3	8.6	10.0	14.0	200	2	S.	D.
46.	43	180/90	24.0	7.0	8.6	16.0	150	7	S.	D.
47.	32	210/110	31.0	12.0	9.2	8.0	170	16	M.	D.
48.	49	190/110	32.0	6.0	10.0	9.0	80	11	S.	I.
49.	36	180/110	26.0	7.0	8.6	12.0	110	27	S.	I.
50.	41	178/120	18.0	9.0	9.5	10.0	120	4	S.	D.

* S.S. severity of symptoms, m. mild, S. severe, M. moderate.
† R. result, I. improved, D. died.

TABLE II

CO_2 Combining Power in Uremia

Vol. %	No. of Cases
77–53	3
53–40	11
40–30	15
30–20	13
20–15	2
Below 15	6

TABLE III

Frequency and Duration of Symptoms of Uremia

Symptoms	Frequency in Chief Complaint	Duration
1. Weakness	40	22 days
2. Vomiting	38	5 "
3. Restlessness	34	9 "
4. Nausea and poor appetite	33	26 "
5. Nocturia	33	3 years
6. Drowsiness	30	3 days
7. Headache	30	68 "
8. Muscular twitching	29	7 "
9. Difficulty in breathing	27	17 "
10. Swelling of ankles	16	19 "
11. Blurred vision	11	34 "
12. Loss of weight	9	96 "
13. Convulsions	7	15 hours
14. Diarrhea	6	5 days
15. Itching	5	12 "
16. Coma	4	7 hours

Acidosis occurs in chronic nephritis because of retention of phosphates and sulphates and the inability of the kidney to elaborate ammonia so that the alkali reserve is depleted by the retained acid. The ultimate course of chronic nephritis leads to death, but at any one time, serious acidosis may exist out of proportion to the degree of structural renal changes. Life may be terminated prematurely, because of acidosis and not because of actual irreparable renal damage. The toxemia is the cause of death. The uremia is an index of renal inadequacy which need not be irreparable.

In table 1 it appears that the severity of the symptoms of advanced nephritis and uremia is directly proportional to the degree of acidosis and not always nor exactly to the extent of nitrogen retention. This table also illustrates the evidence that severe symptoms existed in all instances in which the CO_2 combining power was less than 35 vol. per cent regardless of the degree of nitrogen retention. The symptoms commonly ascribed to nitrogen retention (table 3) are not unlike those characteristic of acidosis from any cause. The majority of the symptoms causing disability were present for a period of less than 30 days prior to admission to the hospital (tables 4 and 5). A consideration of tables 6 and 7 suggests that decrease in CO_2 combining power indicates a greater degree of renal insufficiency than nitrogen

TABLE IV

Uremia

Symptoms Present Less than 30 Days

1. Itching	12 days
2. Difficulty in breathing	17 "
3. Swelling of ankles	19 "
4. Weakness	22 "
5. Nausea and poor appetite	26 "

TABLE V

Uremia

Symptoms Present Less than 10 Days

1. Coma	7 hours
2. Convulsions	15 "
3. Drowsiness	3 days
4. Diarrhea	5 "
5. Vomiting	5 "
6. Muscular twitching	7 "
7. Restlessness	9 "

retention. Tables 1, 6 and 7 show that in advanced nephritis a CO_2 combining power determination is a very valuable index of renal function. It has been found to be more important than the creatinine figure in arriving at a prognosis. The mortality and the duration of life were constantly proportional to the degree of acidosis but not always to the degree of creatinemia. The recognition of the occurrence of acidosis in advanced nephritis is of clinical importance because it offers a therapeutic aid, the use of which may enable the clinician to tide over a patient ordinarily considered hopelessly ill, alleviate serious symptoms or avoid a fatal ending in those cases in which

TABLE VI

The Mortality of Acidosis in Chronic Nephritis

CO_2 Vol. %	Number of Cases	Number of Fatal Cases	Per Cent of Fatal Cases	Days in Hospital
35–25	15	7	46.6	13
25–15	7	6	85.0	5.6
Below 15	6	6	100.0	4.6

TABLE VII

The Mortality of Creatinemia in Chronic Nephritis

Creatinine Mg. per 100 c.c.	Number of Cases	Number of Fatal Cases	Per Cent of Fatal Cases	Days in Hospital
2–5	19	4	21.0	9.2
5–10	22	13	60.0	6.0
Above 10	8	5	62.0	10.0

renal function may be temporarily but not permanently exhausted. Case reports 2 and 12 illustrate this point.

With a creatinine of 8 and 9 mg. per cent respectively in these cases, one ordinarily would be justified in estimating a life expectancy of two or three

Case 2

M. C., female, 49 years of age, admitted to L. I. C. H., December 20, 1933.

Chief Complaint: Restlessness, weakness, heavy breathing, stupor and coma.

Blood Pressure: Systolic 190, diastolic 110; urine: sp. gr. 1.008–1.010, heavy trace of albumin, casts and red blood cells present.

Blood Count: Hemoglobin 68 per cent (Sahli); red blood cells 3,460,000.

Blood Chemistry:	date 12/20	12/25	12/30	2/20
Urea nitrogen, mg. per 100 c.c.	160	140	120	60
Uric acid, mg. per 100 c.c.	7	9.6	7	5.0
Creatinine, mg. per 100 c.c.	9	7.2	10	4.6
Calcium, mg. per 100 c.c.	9.2	—	8	
Phosphorus, mg. per 100 c.c.	13.4	—	7.2	
CO_2(Vol. %)	12.6	40	37.0	44.0

Clinical Diagnosis: Uremia; chronic glomerular nephritis.

Treatment: 300 c.c. 4 per cent sodium bicarbonate intravenously every 12 hours 6 doses; every 24 hours 2 doses: sodium bicarbonate by rectum and later by mouth 60 gr. three times daily.

Result: Chief complaint relieved in 36 to 48 hours, and patient continued free of symptoms except for weakness. She survived for 15 months.

Case 12

R. P., female, 52 years of age, admitted to L. I. C. H., October 22, 1934.

Chief Complaint: Nausea, vomiting, restlessness, muscular twitchings and stupor.

Blood Pressure: Systolic 168, diastolic 90; urine: sp. gr. 1.005–1.011, albumin measurable quantity, casts and red blood cells present.

Blood Count: Hemoglobin 53 per cent (Sahli); red blood cells 3,100,000.

Blood Chemistry:	date 9/25	9/28	10/18	10/22
Urea nitrogen, mg. per 100 c.c.	130	120	75	100
Uric acid, mg. per 100 c.c.	6.6	5.9	6	4.6
Creatinine, mg. per 100 c.c.	8.0	6.7	6	5.0
Calcium, mg. per 100 c.c.	7.0	—	8.0	
Phosphorus, mg. per 100 c.c.	12.4	—	6.2	
CO_2(Vol. %)	13.6	29.0	40.3	41.4

Clinical Diagnosis: Uremia, chronic glomerular nephritis.

Treatment: 250 to 300 c.c. 4 per cent sodium bicarbonate intravenously repeated as indicated by CO_2 combining power every 12 hours.

Result: Stupor relieved in 24 hours. Balance of chief complaint relieved in 5 days. The patient is still living after 2½ years.

months in either instance—but following the correction of the acidosis, the patient described in Case 2 lived 15 months and the one in Case 12 is still alive at the end of two and a half years. In both instances the nitrogen retention diminished with the correction of the acidosis, although in other cases there has been a striking improvement in symptoms but none in the nitrogen retention.

Case 12 illustrates the disappearance of toxic symptoms after relief of the acidosis even though the nitrogen retention persisted.

Case 2 shows a decline in the nitrogen retention after relief of the acidosis.

This phase of the value of correcting the acidosis found in chronic nephritis has been presented in a recent paper.[3] It is of interest here to mention that convulsions did not occur in any of the fatal cases in which the acidosis was corrected, and that one patient lived for six months with an extensive pericarditis, complicating uremia.

In chronic nephritis structural, progressive and irreparable changes are so often present in the kidneys that the term cure cannot be legitimately applied. It may, however, be used for the relief of severe symptoms, such as vomiting, restlessness, drowsiness, which may in some cases constitute the only complaint, or coma, which if unrelieved leads to death.

The existing acidosis, if allowed to remain, not only produces serious symptoms but it deprives the uremic patient of any chance of recovery. If a cure is not possible, relief of symptoms and prolongation of life in such an exceptionally serious condition as uremia are important and valuable.

Conclusions

1. Severe acidosis is a frequent finding in cases of uremia.
2. The symptoms of toxemia in uremia are similar to the symptoms of severe acidosis from other causes.
3. In cases of uremia without severe acidosis subjective symptoms are mild.
4. In cases of uremia a CO_2 combining power determination is important and serves as a valuable prognostic aid.
5. In cases of uremia the greater the acidosis the shorter is the duration of life.
6. A CO_2 combining power determination in advanced nephritis is a valuable test of renal function.

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THE AZORUBIN S TEST OF LIVER FUNCTION; AN EVALUATION, WITH A COMPARATIVE STUDY OF THE BROMSULPHALEIN AND HIPPURIC ACID TESTS *

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Few tests of liver function have proved to be of much value in the diagnosis and prognosis of diseases of this organ. Common to all is the failure to detect hepatic disease in its earlier stages. The multiplicity of the liver's functions, as well as its great regenerative capacity and functional reserve, provides ample explanation for this shortcoming. Although a better understanding of the condition of the liver may be derived from a combined study of several hepatic functions, any test which might elicit more trustworthy information concerning a single function deserves further investigation.

Azorubin S,† a dark red, stable, water soluble dyestuff of the mono-azo group, was first introduced as a test of hepatic function by Tada and Nakashima [19] in 1924. They injected it intravenously and, by duodenal intubation, observed the color changes in the bile. In normal subjects as much as 95 per cent of the dye was excreted in the bile, the remainder being eliminated in the urine. Thus, renal disturbances can exert only a negligible influence upon its excretion by the liver. A delay in appearance of dye in the bile, or a prolonged urinary excretion, was regarded as of pathologic significance. It was found to be harmless and devoid of untoward effects, and when compared with 62 other dyes, yielded more reliable results (bromsulphalein was not included in their study).

Fenstermann (1926) [3] observed a close parallelism between the extent of liver damage and the impairment in the hepatic excretion of azorubin S. Studying patients with "catarrhal jaundice," atrophic cirrhosis and cholecystitis, Lebedow (1930) [5] found the test a very useful and reliable index of liver function. When the clinical manifestations of catarrhal jaundice were maximal no dye was eliminated in the bile, whereas the urine remained deeply colored for as long as 24 hours. Regression of the syndrome was marked by the reappearance of biliary dye. Cirrhosis uniformly manifested a delayed hepatic excretion. Nakashima (1934) [7] noted several instances of liver disease in which the dye excretion was accelerated, and suggested that this response might be due to a "compensatory hyperfunction"

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† The Azorubin S solution used in this study was prepared by George A. Breon & Co., Kansas City, Missouri.

of the liver. Weiss (1935),[21] in his studies, found azorubin S preferable to bromsulphalein. More recently, Eppinger (1937)[2] corroborated the findings of the earlier investigators and extolled the virtue of the azorubin S test. He considered it of greatest value in the differentiation of "catarrhal" from parenchymatous jaundice, the presence of bile-stained duodenal contents in the absence of biliary dye indicating the latter form. In some cases of suspected liver damage without icterus the azorubin S test was unique in its detection of impaired function.

Such enthusiastic reports merit further confirmation and study. We have, therefore, performed the azorubin S test on 14 normal subjects and on 27 patients with hepatic disease. The results in the latter group are compared with those of the bromsulphalein test, generally regarded as the most satisfactory test of the excretory function in patients without clinical jaundice; and with those of the hippuric acid test, which determines the detoxifying function of the liver, and is reported to be reasonably accurate in the diagnosis and prognosis of disease in individuals with manifest jaundice.[16]

Methods

Azorubin S Test. After an overnight fast, a narrow flexible tube is passed into the duodenum and its position confirmed fluoroscopically. When bile begins to flow through the tube, 4 c.c. of a sterile 1 per cent aqueous solution of azorubin S are injected intravenously. Five minutes later, 40 c.c. of 25 per cent aqueous magnesium sulfate solution are administered through the duodenal tube. The duodenal contents are collected in separate test tubes at one to two minute intervals, and the time elapsing between the injection of the dye and the appearance of a very deep red efflux is designated as the "appearance time." For color determinations and comparisons the best results are obtained by observing the solutions in bright daylight; slanting the tube against a white background is also helpful.

Using a colorimetric method, Zinny (1926)[23] measured the amount of dye excreted in the bile, and found that an excretion of less than 0.01 gm. in one hour is significant of liver damage. Although perhaps more accurate, this method seemed unnecessary. Fenstermann[3] preferred a simple colorimetric examination of the urinary dye, but this procedure proved unreliable in our hands.

Hippuric Acid Test. The technic was that originally described by Quick,[10] "method 1" being used for the quantitative analyses. In accordance with the modification of Kohlstaedt and Helmer,[4] the hourly specimens of urine were pooled and a single determination made. An excretion of 3 gm. of hippuric acid, in terms of benzoic acid, was considered normal, with 85–115 per cent of this value as the normal range.[10]

Bromsulphalein Test. The method was similar to that described by Rosenthal and White,[14] except that the amount of dye injected intravenously

was calculated on the basis of 5 mg. per kilogram of body weight.[8, 12] A single sample of blood was drawn 30 minutes after administration of the dye. From our observations on normal subjects, a retention of more than 10 per cent may be regarded as abnormal.

In all cases the tests were performed on successive days, in order that the results might be comparable.

Results

Normal Subjects. In normal individuals Tada and Nakashima[19] observed a very deep red discoloration of the bile 17 to 18 minutes after injection of azorubin S. Fenstermann[3] found the range of normal to be 15 to 30 minutes, while Eppinger[2] considered it to be 15 to 20 minutes. In their study on arthritis Rawls, Weiss and Collins[11] accepted 15 to 30 minutes as the normal range.

In order to become familiar with the normal limits of variation, as well as to define them more precisely, the azorubin S test was performed on 14 normal subjects. Usually a succession of color changes in the bile was noted in the following order: orange, reddish-orange, light red, light cherry red and deep cherry red, after which the color faded out in the reverse order. The appearance time of the significant test color (deep cherry red) ranged from 17 to 29½ minutes, whereas the first appearance of dye, however faint, varied from eight to 25 minutes (table 1). In three individuals, a burgundy wine color followed the deep cherry red and was observed 22½, 26½ and 27 minutes, respectively, after injection of the dye. In three subjects (numbers 4, 8 and 12) very dark brown bile (B bile) appeared after injecting magnesium sulfate. This, when stained by the dye, resembled a burgundy wine hue; but within five to seven minutes the bile became lighter

Table 1

Results of the Azorubin S Test in Normal Subjects

Subject	First Appearance of Biliary Dye (Minutes)	Appearance Time of Deep Cherry Red Bile (Minutes)	Comment
J. M.	10	19	
B. D.	16½	23½	
B. F.	8	18	
S. B.	20	29½	
D. V.	25	26	
G. M.	23½	29	
P. B.	15	17	
O. M.	15	20	
M. P.	17	27	
J. G.	16	29	
N. S.	13½	20½	Burgundy red—22½
F. M.	13	24	Burgundy red—27
J. B.	21	26	
W. L.	20½	24	Burgundy red—26½

in color and an accurate reading could easily be made. This incident was not encountered in any of our abnormal cases.

From the foregoing observations, and in agreement with the standard accepted by Rawls, Weiss and Collins,[11] the normal appearance time of a deep cherry red color was regarded as 15 to 30 minutes.

Hepatic Cirrhosis. Nineteen patients with cirrhosis were studied (table 2). Of these, 18 were in the hypertrophic stage and one was in the atrophic stage. The edge of the liver in the hypertrophic group extended 6 to 10 cm. below the costal margin in the mid-clavicular line on deep inspiration; the consistency was increased and the surface was smooth in all but three instances (numbers 1, 5 and 8). The spleen was palpable in 15 cases, and in the majority was only slightly enlarged. No patients with ascites were chosen for this study, for it was our intention to select individuals presenting less advanced grades of cirrhosis without portal decompensation. It was realized, of course, even in the absence of the latter phenomenon,

TABLE II

Comparative Results of the Azorubin S, Bromsulphalein and Hippuric Acid Tests

Patient	Diagnosis	Azorubin S Appearance Time (Min.)	Bromsulphalein Retention %	Hippuric Acid Excretion		Icterus Index	A/G	Comment
				Benzoic Acid Gm.	Excretion %			
1	Syphilitic cirrhosis	60	40	2.12	71	5	3.95/2.65	N.P.N. 38 P.S.P. Test—17%
2	Hypertrophic cirrhosis	∞ (41)	40	2.78	93	12	—	Cholesterol esters 112 Cholesterol total 252
3	Hypertrophic cirrhosis	∞ (54)	90	1.46	49	55	2.9/3.4	N.P.N. 24 Cholesterol total 320 Cholesterol ester 98 Macrocytic anemia
4	Hypertrophic cirrhosis	46	20⁻	3.29	110	9	—	N.P.N. 27
5	Hypertrophic cirrhosis (biopsy)	∞ (90)	70	—	—	22	2.8/4.7	Phosphatase 23 units Cholesterol total 154 Cholesterol esters 38 Macrocytic anemia
6	1. Hypertrophic cirrhosis 2. Cholelithiasis	41	40	3.46	115	5	—	Cholesterol total 166 Cholesterol esters 62 N.P.N. 41 Cholesterol and calcium bilirubinate crystals in bile
7	Hypertrophic cirrhosis	∞ (71)	20	—	—	20	—	Phosphatase 16 units
8	Hypertrophic cirrhosis (biopsy)	∞ (60)	30	2.42	81	13	—	N.P.N. 27 Cholesterol total 210 Cholesterol esters 93
9	Hypertrophic cirrhosis	51	40	3.14	105	10	—	N.P.N. 31
10	Hypertrophic cirrhosis	35	10	3.44	115	6	—	N.P.N. 31 Cholesterol total 189
11	Hypertrophic cirrhosis	36	20+	2.90	97	11	—	N.P.N. 30
12	Hypertrophic cirrhosis	45	30	1.59	53	6	—	N.P.N. 40
13	Hypertrophic cirrhosis	42	20+	3.10	103	7	—	Urea N 17

TABLE II—*Continued*

Patient	Diagnosis	Azorubin S Appearance Time (Min.)	Bromsulphalein Retention %	Hippuric Acid Excretion		Icterus Index	A/G	Comment
				Benzoic Acid Gm.	Excretion %			
14	Hypertrophic cirrhosis	∞ (54)	60	3.13	104	8	—	N.P.N. 30
15	Hypertrophic cirrhosis	∞ (45)	50	1.14	38	12	—	N.P.N. 29 Cholesterol total 145 Cholesterol esters 36
16	Hypertrophic cirrhosis	33	50	3.80	127	—	—	N.P.N. 25
17	Hypertrophic cirrhosis	∞ (60)	100	2.89	96	15	4.0/2.25	N.P.N. 26
18	Hypertrophic cirrhosis	37	70	2.62	87	5	5.15/3.05	N.P.N. 35
19	Atrophic cirrhosis	∞ (52)	90	1.12	37	22	1.83/3.27	N.P.N. 38 Cholesterol total 208 Cholesterol esters 113 Macrocytic anemia
20	Chronic hepatitis	33½	5	3.39	113	9	—	N.P.N. 29
21	Chronic hepatitis	∞ (70)	10	3.46	115	5	—	N.P.N. 33
22	Chronic hepatitis	∞ (64)	5	2.99	100	—	—	N.P.N. 29
23	1. Chronic hepatitis 2. Cholelithiasis	37	20	4.01	134	5	—	N.P.N. 26 Cholesterol and calcium bilirubinate crystals in bile
24	Subsiding acute hepatitis	26½	20	—	—	22	—	Van den Bergh—direct and indirect immediate positive
25	Acute toxic hepatitis	34	50	2.33	78	24	—	N.P.N. 34
26	Acute toxic hepatitis	∞ (45)	100	3.13	104	36	—	N.P.N. 29
27	1. Fatty metamorphosis of liver 2. Diabetes mellitus	35	20	1.48	49	5	—	N.P.N. 38 Cholesterol total 176

∞—indicates that the biliary drainage never became deeper than an orange red or pale red color. The length of the observation period following dye injection is shown in parentheses.
P.S.P.—Per cent phenolsulphonephthalein excretion in 1 hour (intravenous method).

that the disease, strictly speaking, is usually not in an early stage by the time the clinical diagnosis has become unequivocal.

The azorubin S test was positive in all 19 patients, the appearance time being definitely delayed in each case (table 2). In nine instances, the bile never acquired more than a reddish orange or pale red color. Serum albumin and globulin determinations made on five of these nine patients revealed a reversal of the A/G ratio in four, thus indicating a more advanced stage of hepatic disease. Indeed, those individuals presenting a harder, larger or more diffusely involved liver, generally, though not invariably, manifested a greater delay in hepatic excretion. Three of the four patients with a lowered serum albumin fraction also exhibited a macrocytic anemia. The urine, which normally is discolored for three to 11 hours after injection of the dye,[19, 3, 5] and which, in hepatic disease, has been observed to remain colored for proportionately longer periods, was of no value as an indirect measure of liver damage in the three patients studied in this manner. In

patient 1, the dye never appeared in the urine; in patient 23, it had disappeared within four hours; and in patient 2, within six hours.

The bromsulphalein test was positive in 18 out of the 19 patients, comparing exceedingly well with the azorubin S test. Excluding the single bromsulphalein failure, a case of Banti's syndrome, the azorubin S test was more strongly positive than the bromsulphalein in two patients (numbers 4 and 7), whereas in two others (numbers 16 and 18) the converse held true. In general, however, the bromsulphalein retention in this group paralleled the delay in azorubin S excretion.

The hippuric acid test, performed on 17 patients, proved disappointing. Positive results were obtained in only six instances, and in these bromsulphalein and azorubin S tests were strongly positive. In the remaining 11 individuals, negative to the hippuric test, the azorubin S test was uniformly positive, whereas the bromsulphalein test was positive in 10.

Other Forms of Hepatic Disease. Under this heading are included two cases of acute toxic hepatitis, one of subsiding acute hepatitis, one biopsy-proved case of marked fatty metamorphosis of the liver associated with diabetes mellitus, and four cases of relatively early, mild chronic hepatitis.

The azorubin S and bromsulphalein tests were positive in the two patients with toxic hepatitis, whereas the hippuric acid test was negative in one of these. In the patient with subsiding acute hepatitis, the bromsulphalein test was positive and the azorubin S test negative, but the significance of the bromsulphalein response is difficult to evaluate, since unreliable results are often obtained with this dye in cases of jaundice, particularly if the Van den Bergh reaction is direct.[18] All three tests were positive in the individual with fatty metamorphosis of the liver.

The four patients with chronic hepatitis are noteworthy from a diagnostic and therapeutic standpoint. They had been observed by able clinicians prior to these studies, yet, as not infrequently happens in these cases, the possibility of an hepatic disorder apparently had received little if any consideration. The histories being suggestive of biliary tract disease, cholecystograms and roentgenographic studies of the gastrointestinal tract had been made. In three patients normal findings had been reported and the symptoms ascribed to a "functional" disorder. In the fourth patient (number 23) cholelithiasis was suspected but could not be substantiated during the earlier period of observation. All 4 patients presented a slightly enlarged liver of somewhat increased consistency, which was tender on moderate pressure and on fist percussion; in two of them the spleen was just palpable on inspiration. We strongly suspected liver disease (chronic hepatitis), but the diagnosis needed corroboration. Significantly, the azorubin S test was positive in all four instances. The bromsulphalein test was positive in only one, and the hippuric acid test was uniformly negative. In accord with our diagnosis of hepatic disease and the results of the azorubin S test, a dietary regimen high in carbohydrate and low in fat was instituted.

The rapid subjective and objective improvement which ensued was most gratifying. The following summarized case history is illustrative:

Case 22. M. L., a white female, aged 33, was seen on April 29, 1937, complaining of heaviness in the epigastrium, bloating and belching of five and one-half years' duration. A recent diagnostic study done elsewhere (including blood count, Wassermann and Kahn, urinalysis, stool examinations, Ewald test meal, cholecystogram, gastrointestinal roentgenograms and basal metabolism) revealed no abnormalities. A diagnosis of "nervous disorder" had been made. Bland diet and sedatives were ineffective. The liver edge descended 6 cm. below the costal margin on deep inspiration, was tender on pressure, and of slightly increased consistency. Spleen descended 1 cm. below the costal margin on inspiration. On May 3, the azorubin S test was positive (first discoloration at 31 minutes; maximum intensity—light red at 44 minutes; progressively lighter thereafter). May 4, bromsulphalein test: 5 per cent retention at one-half hour. May 5, hippuric acid test: 2.99 gm. in terms of benzoic acid. Diagnosis: chronic hepatitis. Treatment: high carbohydrate, low fat diet. Within four days subjective improvement was first noted; 10 days later symptoms were "practically absent." Hepatic tenderness subsided rapidly. On January 29, 1938 the liver edge descended 1 to 2 cm. below the costal margin on deep inspiration.

The Azorubin S Test Combined with a Crystallographic Study of the Bile. Piersol, Bockus and Shay,[9] Shay and Riegel[15] and others have demonstrated the value of a microscopic study of bile in the diagnosis of cholelithiasis, indicating its superiority over the roentgenogram. They pointed out that the presence of both cholesterol and calcium bilirubinate crystals is pathognomonic, whereas the finding of only one of these elements is strongly in favor of gall stone disease. These observations have been confirmed by Bloch and Rosenberg.[1] Lyon[6] and others have also emphasized the value of a cytologic study of bile in the diagnosis of cholecystic disease. The technic of the azorubin S test lends itself to a combined study of liver function and composition of the bile. For the latter purpose the bile collected before and after injection of magnesium sulfate, prior to the appearance of the dye, may be utilized. In the present study we have searched for crystals in the bile in selected cases.

The coexistence of cholelithiasis with hepatic cirrhosis is not uncommon, the reported incidence being as high as 13 per cent.[13] Upper abdominal pain may be the predominating symptom in either disease, yet the finding of a non-visualizing gall-bladder cholecystographically may be of no diagnostic significance in the presence of cirrhosis, often leading to erroneous conclusions. In these cases the establishment of the presence of calculi, which is important therapeutically, may be impossible without a crystallographic study of the bile. The advantage of a combined liver function test and bile examination is illustrated by the following case abstract:

Case 6. M. P., a white male, aged 64, married, was seen on June 22, 1937, complaining of nausea, mild and severe attacks of epigastric and right hypochondriac pain, progressive loss of weight (15 kg.), weakness and constipation of three years' duration. Examination revealed a well developed, poorly nourished male. The liver edge was 10 cm. below the costal margin on inspiration, sharp, tender, and of increased consistency. Spleen: edge smooth, rounded, of increased consistency, and

6 cm. below the costal margin on inspiration. Blood count normal. Ewald test meal: free HCl, 29, total acidity, 56. Gastrointestinal tract normal roentgenographically. Three cholecystograms revealed no visualization of the gall-bladder. A diagnosis of hepatic cirrhosis was made. Cholelithiasis was suspected but could not be proved. December 20—Bromsulphalein test: 40 per cent retention in 30 minutes. December 21—azorubin S test: positive (appearance time—41 minutes). The bile, collected following magnesium sulfate instillation, was centrifuged for 20 minutes. Microscopically the sediment showed large numbers of cholesterol and calcium bilirubinate crystals, denoting calculi. Accordingly, a high carbohydrate regimen followed by cholecystectomy was recommended, but the latter was refused by the patient.

In this instance the technic of the azorubin S test, as utilized by us, served a dual purpose: first, that of measuring the function of the liver, and second, that of disclosing evidence of calculi.

The importance of a preoperative study of liver function in cases of cholelithiasis and cholecystitis is now generally appreciated. That the combined method under consideration may be useful in recognizing latent forms of hepatic insufficiency, and in detecting or corroborating the presence of calculi, is shown by the following case abstract:

Case 23. I. R., a white female, aged 63, was seen on June 2, 1937, complaining of nausea, heartburn, belching, bloating, epigastric pain and constipation of "many" years' duration. Examination revealed a well developed, well nourished woman. The liver edge was 5 cm. below the costal margin in the mid-clavicular line on deep inspiration, sharp, of increased consistency and tender on pressure. Spleen: edge just palpable on inspiration. Histamine fractional gastric analysis: free HCl, 0; total acidity, 10. Roentgenographic studies of the gastrointestinal tract showed multiple diverticula of the colon and hypermotility of the sigmoid. Cholecystogram: Normal except for a questionable translucent area in the gall-bladder shadow. Bromsulphalein test: 20 per cent retention in 30 minutes. Azorubin S test: positive (appearance time, 37 minutes). Microscopic examination of the bile sediment revealed many cholesterol and calcium bilirubinate crystals. In the light of these findings, a diagnosis of cholelithiasis with chronic hepatitis was made. The cholecystogram was then repeated and showed positive evidence of at least two gall stones. The indications for medical management, directed toward the hepatitis, followed by cholecystectomy were thus clearly evident.

Comment

The value of the bromsulphalein test in recognizing widespread or moderately advanced liver disease has already been established. Hence, its close agreement with the results of the azorubin S test in our patients with cirrhosis and acute hepatitis, particularly the former, may be regarded as confirmatory evidence of the reliability of the azorubin S test in such conditions. Moreover, the detection of lesser degrees of hepatic insufficiency (chronic hepatitis) by the azorubin S test, in the face of bromsulphalein failures (three out of four cases), is significant and concurs with the experience of Eppinger.[2] However, in view of the small number of such cases studied, our results are suggestive but not conclusive as to the superiority of the azorubin S test. In accord with the observations of Fenstermann,[3] a rough parallelism between the delay in hepatic excretion of azorubin S and

the degree of liver damage is discernible in our series. In none was the dye excreted more rapidly than normal. Further, the urinary excretion of azorubin S as an indirect test of liver function, originally proposed by Tada and Nakashima [19] and extended by Fenstermann [3] and Lebedow,[5] is untrustworthy as shown by Eppinger [2] and early in our work.

The added merit of a liver function test which permits simultaneous microscopic study of the bile should not be underestimated. As exemplified by patients 6 and 23, the technic of the azorubin S test is well adapted for this procedure, and may prove valuable in cases of cholelithiasis both from a medical and a surgical point of view.

The discordant results obtained with the hippuric acid test, as compared with those obtained with the other tests, were most surprising. Of 24 cases thus studied, 17 of which were cirrhosis, 15 were negative. Comparing the hippuric acid and bromsulphalein tests in three patients with decompensated portal cirrhosis and in three individuals with obstructive jaundice, Snell and Plunkett [17] found the former test positive in five and the latter positive in all six. Vaccaro [20] considered the hippuric acid test "more accurate" than bromsulphalein, but little reliance can be placed on this phase of his investigation, because of the small number of comparable cases studied with the bromsulphalein test, the lack of uniformity in the technic of the latter as employed in different patients, and because his range of normal values for hippuric acid excretion is now regarded as too narrow. From a review of the literature,[4, 10, 17, 20, 22] it is apparent that a large proportion of the reported cases of cirrhosis studied with the hippuric acid test presented a far advanced stage of the disease. There was either a reversal of the albumin-globulin ratio or portal decompensation, or both. This may explain the discrepancy between former reports and our own. If this explanation is correct, the usefulness of the hippuric acid test is restricted to patients with the more advanced grades of chronic disease without adequate hepatic regeneration, or to those with more acute, diffuse damage, either initial or in a state of exacerbation. Our findings would seem to indicate that the integrity of the detoxifying function of the liver remains intact longer than has been hitherto appreciated.

Finally, like many other tests, the azorubin S test has certain disadvantages. The obvious practical objection is that duodenal intubation may be time consuming and should be accompanied by fluoroscopic observation of the tube in situ. It is also essential that the examiner become well acquainted with the normal for the proper interpretation of this test in the abnormal. Nevertheless, should the test prove as useful as the trend of our results indicates, its disadvantages would be far outweighed by its advantages.

Summary

1. The azorubin S test of liver function, which has received little attention in this country, was performed on 14 normal subjects; and a compara-

tive study of this test with the bromsulphalein and hippuric acid tests was made in 19 cases of cirrhosis, two cases of acute toxic hepatitis, one case of subsiding acute hepatitis, one case of fatty metamorphosis of the liver and four cases of relatively early chronic hepatitis.

2. The azorubin S test was found to be as reliable as the bromsulphalein test and better than the hippuric acid test in cases of cirrhosis.

3. In the cases of relatively early chronic hepatitis, the azorubin S test was superior to both the other tests.

4. Although the azorubin S test requires duodenal intubation, the method lends itself to a simultaneous crystallographic study of the bile. Illustrative cases are cited in which the combined technic was used to advantage.

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THE PROBLEM OF RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1938

(Sixth Rheumatism Review)*

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In Two Parts

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Part I

General Incidence of Rheumatic Diseases; Social and Economic Importance

In our preceding Review [5] were given preliminary data from the National Health Survey indicating that "rheumatism" was by far the most common chronic disease in the United States, and ranked second in producing both temporary and permanent disability. Further data from this survey have appeared.[970-975] Conducted by the United States Public Health Service, the survey involved a house-to-house canvass of about 800,000 families comprising about 2,800,000 persons in 83 cities and 23 rural areas of 19 states. Among 2,152,741 white persons questioned were 11,997 whose sole or primary cause of disability was rheumatism: of these, 592 were under 15 years of age, 560 were aged 15 to 24 years, 7,953 were aged 25 to 64 years, and 2,892 were older. Over 50 per cent (6,358 persons) were from poor families: 3,079 were on relief, 3,279 were members of families whose annual income was under $1000.00.[975]

The incidence of "rheumatism and allied diseases" on a given day in the United States was estimated to be about one (0.099 per cent) per 1000 persons.[972] The incidence per 1000 persons according to age and sex was as follows: less than 0.05 for persons under 15 years of age; 0.9 among those aged 15 to 64 years, and 5.4 for those aged 65 years or more. The incidence per 1000 females of all ages was twice that for males. It was 1.2 for females of all ages, negligible for those under 15 years of age, 1.1 for those aged 15 to 64 years, and 6.6 for those older. The incidence per 1000 males was 0.6 for those of all ages, negligible for those under 15 years, 0.6 for those aged 15 to 64 years, and 3.8 for those older.[972]

Applying these figures to the total population it was estimated that there were 6,850,000 cases of rheumatism in the United States in 1937, or more than the *total number* of all cases of heart disease, cancer and other tumors, tuberculosis and diabetes. Rheumatism caused an annual loss from work of 97,200,000 days, and produced 147,600 permanent invalids. The mortality from rheumatism was 3.4 per 100,000 persons [973] and among chronic diseases rheumatism ranked fourteenth as a cause of death.

[It is difficult to compare these statistics with those noted in previous Reviews. In 1933 the Massachusetts survey indicated an incidence of 3,264,000 persons with chronic rheumatism in the United States. In 1936 Kling [4] estimated that there were 2,700,000 patients with chronic rheumatic diseases in the country. In this National Health Survey rheumatism was broadly defined and included "rheumatism, arthritis, gout, neuralgia, neuritis, lumbago, acute rheumatic fever, stiff neck and other muscular pains." [975] For various reasons the survey has been subjected to considerable criticism.[110, 977] The field work was done by about 7000 canvassers drawn from the relief rolls of the Works Progress Administration and included former salesmen, nurses, teachers, social workers and so forth. All were given at least a week of preliminary intensive training for their work. In 350,000 instances the diagnoses were confirmed by later inquiries from attending physicians.[970] Even so it is difficult to believe that the diagnoses of rheumatism were accurate. Differentiation of the rheumatic diseases is difficult enough for physicians and well nigh impossible for laymen. Hence some critics [110] have discounted the accuracy of this "doorbell survey conducted by W. P. A. laymen." In the present state of our knowledge of the rheumatic diseases no survey would be any too accurate even if canvassers were physicians. But at least these figures indicate again that the rheumatic diseases are very prevalent in the United States.—Ed.]

A few new statistics were reported from other countries. Davidson and Rae stated that in 1936 there were among the insured population of

Scotland (35 to 40 per cent of the total population) "no fewer than 50,000 cases" of rheumatism in its various forms which caused the huge total of 3,500,000 days' incapacity. This entails an annual economic loss of two or three million pounds. It was estimated that in Scotland 334,872 new cases of rheumatism develop annually.

From the statistics of the National Health Insurance Society of Ireland O'Reilly attempted to make the first survey on the incidence of rheumatism in that country. Among an insured population of 500,000 persons were 16,000 who claimed disability because of rheumatism during 1935. Rheumatism was responsible for the greatest number of claims, the largest amount of money paid out in claims (131,000 pounds) and the greatest amount of incapacity (295,000 weeks in the year) of all diseases in Ireland.

According to Finn there are great numbers of cases of chronic rheumatism or arthritis in South Africa, probably as many as in other countries whose statistics have been reported. This gives further evidence that this disease-group is a world wide scourge. The influence of industry, occupation and housing on the incidence of the rheumatic diseases in various countries was discussed in detail (Conybeare and Glover; Fox; Van Breemen). Exposure to cold and to occupational fatigue were considered to be more important factors than others, e.g., humidity.

Definition of Rheumatism; Content of "the Rheumatic Diseases"

"Rheumatism" and the rheumatic diseases have never been adequately defined. Current literature does not clarify the terms. The origin of the term "rheumatism" and the history of the various forms of "chronic rheumatism" were outlined by Rolleston in a scholarly paper which will serve as an excellent source of original references and will especially interest those concerned with the genealogy of the rheumatic diseases. The relationship of the various rheumatic diseases to one another was discussed by Poynton,[772] and the French concept of "arthritisme" was defined by Bezançon and Weil. According to Fox[328] chronic rheumatism includes separate but allied diseases the earliest common feature of which is a characteristic abnormality in the patients' reactions to changes in external environment, especially to cold. Since there is no known common pathologic lesion to identify rheumatic disease, the authors of this Review will, as previously, use the layman's broad anatomic concept of rheumatism and will discuss herein a wide variety of diseases of joints and related structures.

Classification of Diseases of Joints and Related Structures

Recently few writers have indulged in new classifications of the rheumatic diseases. Ellman discussed the merits and demerits of several classifications. The year's literature presented a few minor revisions of older classifications not important enough for extended comment here.

Among them was O'Connor's classification based on the assumption

that the three basic etiologic factors in arthritis are bacteria, toxins and trauma. A first group "infectious arthritis" was separated into two subdivisions (*a*) "bacterial arthritis"; use of this term was restricted to forms in which there is actual intra-articular invasion of identifiable bacteria, and (*b*) "toxic (infectious) arthritis" presumably due to a variety of bacterial poisons. A second group "non-infectious toxic arthritis" included those presumed to arise from (*a*) endogenous toxins ("intestinal or glandular dysfunction") and (*b*) exogenous toxins from food, medicines, biologic materials or industrial poisons.

[This classification possesses the same merits and demerits as those of other etiologic classifications, chief objection being that no *identifiable* toxins from bacteria or from "intestinal or glandular dysfunction" have ever been isolated and proved to be the cause of any form of human arthritis.—Ed.]

Relative Frequency of the Rheumatic Diseases

Published data on the relative incidence of the rheumatic diseases vary greatly depending on the writer's practice, whether he is a general practitioner, or a physician supervising a clinic for ambulatory rheumatism patients or a spa. According to Davidson's estimate the 334,872 new cases of rheumatism developing in Scotland annually include 26,030 cases (7.7 per cent) of rheumatic fever, 20,284 cases (6.1 per cent) of rheumatoid arthritis, 31,382 cases (9.4 per cent) of osteo-arthritis, and 251,176 cases (76.8 per cent) of muscular rheumatism. The order of frequency of rheumatic and allied conditions among the insured Scottish population of Aberdeen and Kincardine counties was as follows (Rae): lumbago 810 cases, rheumatism (undefined) 724, muscular rheumatism 682, synovitis and bursitis 368, sciatica 221, arthritis (unspecified) 185, "subacute and [acute?] articular rheumatism" 93, "muscular (non-rheumatic)" 88, "chronic joint changes" 65, rheumatoid arthritis 25, osteo-arthritis 18 and brachial neuritis 16, a total of 3295 cases among 126,633 insured persons.

[Because of the vague diagnoses these statistics are not very useful except to indicate that nonarticular rheumatism was much more frequent in that locality than arthritis. Either the incidence of rheumatoid and osteo-arthritis was surprisingly low or criteria for its recognition were poorly understood. And do Scots no longer have gout?—Ed.]

Having treated about 5000 cases of rheumatism O'Reilly concluded that in any 100 cases of rheumatism 48 patients will have fibrositis, 32 rheumatoid arthritis, 13 osteo-arthritis, 5 gout and 2 ankylosing spondylitis.

[This ratio differs somewhat from that of one of us (P. S. H., 1935) who estimated that among 100 "rheumatism patients" seen in general office or clinic practice 30 to 40 would have atrophic (rheumatoid) arthritis, 25 to 30 hypertrophic (osteo-) arthritis, at least 10 to 20 fibrositis of various types, 7 to 10 traumatic (including static or "micro-traumatic") arthritis, 3 to 5 gouty arthritis, 3 to 5 miscellaneous types (arthritis with psoriasis, tuberculosis, ulcerative colitis, syringomyelia, etc.), 2 gonorrheal arthritis and rheumatic fever. In the arthritis clinic of the Presbyterian

Hospital, New York, the relative percentages are approximately as follows: hypertrophic arthritis 30, atrophic arthritis 25, nonarticular rheumatism 20, traumatic and postural arthritis 10, rheumatic fever 5, gonococcal arthritis 3, gout 1, miscellaneous 6 (M. H. D.). In general hospital practice the proportion of cases of rheumatic fever is usually higher than in general office or clinic practice.—Ed.]

Diseases of Joints Related Primarily to Trauma

Sprains and Strains. Various types of sprains and strains, and methods for their diagnosis and treatment were reviewed.[285] To understand the mechanism for the production of sprains one must remember that there are three types of articular ligaments: (1) those which consist of simple thickenings of capsule, which thickenings are too indefinite to be defined by dissection (e.g., internal lateral ligaments of knees and ankles; indeed most articular ligaments); (2) extracapsular bands which, when dissected, stand out as isolated structures (e.g., external lateral ligament of knees; middle and posterior fasciculi of external lateral ligament of ankle); (3) intra-articular bands (e.g., crucial ligaments of knees; ligamentum teres of hips; intra-articular fibrocartilage of sternoclavicular joints).

Ligaments of type 1 rarely rupture completely unless subjected to forces sufficient to produce articular dislocation. When such ligaments are sprained, lesions generally occur at bony attachments, and no articular instability or hypermobility results. For such sprains Elmslie recommended the use of firm elastic pressure to prevent or reduce effusions, rest of the part for 24 hours, then application of adhesive bandages and use of the part; after seven days the adhesive strapping is removed, then massage and active, and if necessary, assistive movements are used. A sprain-fracture occurs when a portion of bone at the ligamentous attachment is pulled off. It may occur especially in fingers and at the femoral attachment of the internal lateral ligament of the knee. A variety of the latter is the Pellegrini-Stieda disease. When sprain-fractures affect fingers or toes, the part should be securely strapped; limited motion is allowed but massage avoided. Only after six or more weeks when swelling and tenderness have subsided should the strapping be removed and motion begun. For knees so affected compression bandages, gentle exercises and faradic stimulation were recommended.

[The time for healing varies with the severity of the injury. Children's ligaments heal rapidly.—Ed.]

When ligaments of types 2 and 3 are strained sufficiently to be ruptured, articular instability may result. When conservative measures (application of splints or plaster with the joint in a position to relax the affected ligament, and other measures) fail, surgical procedures to repair the ligaments are indicated.

Internal and Other Derangements of Knee Joints. Knee joints are most commonly affected by injury. Several papers reviewed the anatomic relationships of the knee joint and the differentiation of the common types of

internal derangement.[75, 178, 469, 470, 563, 660, 754, 778] The common internal derangements and associated lesions of knee joints were listed as follows: (1) injuries (displacement or fractures) of the internal or external semilunar cartilages (menisci), (2) fractures of tibial spine, (3) fractures of tibial tuberosity, (4) strains or ruptures of crucial ligaments, (5) strains or ruptures of lateral ligaments, (6) damage to the retropatellar fat pad, (7) loose bodies in the knee joint which generally result either from osteochondritis dissecans, osteochondromatosis or synovial enchondromata, (8) patellar fracture, (9) slipping patella (not truly an internal derangement but a condition which may occur with mild knock knees and may produce locking). According to Chatterton the conditions numbered 1, 2, 3, 6, 7 and 9 are likely to cause locking, the others (numbers 4, 5 and 8) are not. To the above list of internal derangements, most of which are produced by acute trauma, the Penns added several nontraumatic internal derangements. Bennett described in detail two unusual derangements: a large cyst of the subpatellar fat pad and a large fibrochondroma of the subpatellar fat pad.

Anatomic studies on the relative importance of the cruciate and collateral ligaments in maintaining the stability of knee joints were made by Horwitz and Davidson.[469, 470] They confirmed the opinion of others that the lateral ligaments, especially the internal, are chiefly responsible for preserving the intrinsic stability of the extended knee, and that the cruciate ligaments are of secondary importance and are not indispensable to stability of knee joints. Hence after articular trauma, the integrity of a knee is not markedly altered if cruciate ligaments alone are torn or excised, provided collateral ligaments remain intact. Thus, articular stability can be restored simply by repairing the injury to collateral ligaments and disregarding the cruciate ligaments. Mauck's operation for repairing collateral ligaments was recommended and described.

Various methods for the surgical and nonsurgical treatment of internal derangements were reviewed.[75, 178, 563, 754, 778] The joint should be given a chance to heal without surgical interference. If symptoms persist, or disappear only to return repeatedly, then only should surgical intervention be considered. Trivial lesions of articular cartilage produce no permanent disability. [But over a period of years they may predispose to or induce degenerative changes.—Ed.] After severe injury pieces of cartilage may be torn loose and remain viable for long periods as intra-articular loose bodies which generally must be removed. Damaged intra-articular fat pads may also have to be removed. Intra-articular fractures generally heal, but injury to synovial membrane may result in synovial thickening and villous formation. [It is the belief of one of us, A. J. K., that after trauma the synovial membrane heals promptly. Thickening and villous formation are due to arthritis caused by damage to articular cartilage which does not heal, and disorganization of the joint resulting from the healing of bone with incongruity of articular surfaces.—Ed.] Since semilunar fibrocartilages of knees possess no blood vessels except at their junction

with the coronary ligaments, these cartilages when injured do not repair satisfactorily, and their surgical correction is generally necessary.[178, 563]

Frequent locking of knees provides a special hazard for city dwellers which has often led to minor and major injuries, even to skull fractures; hence the condition should be corrected fairly early.

Tennis Elbow. This subject was well reviewed by Higgs, North, and West. The condition may affect tennis players and those in other sports or at certain occupations which involve forcible extension and supination of the elbow combined with a clenched hand. It rarely affects persons under 30 to 35 years of age. Symptoms were described in our First Review.[1]

> The typical pain is felt in the region of the external epicondyle of the humerus and extends down the back of the forearm to the wrist. It is produced by movements involving sudden contraction of the radial extensors, and can be reproduced by Mill's test which consists in putting fingers and wrist in full flexion and pronation, and then extending the elbow. There is tenderness over or near the anterior aspect of the external epicondyle. When the patient pronates his forearm and extends his wrist to grasp even some light object, sudden weakness may cause him to drop it. Objectively the elbow appears normal, and when it is moved passively pain and stiffness are absent. No abnormality is indicated in roentgenograms.

The major factor is trauma. Symptoms may begin rather promptly but generally appear slowly a few days after acute direct or indirect injury. Marked differences of opinion exist as to the pathologic basis. Carp[1] and Cyriax[3] collected 26 different views thereon. With the majority of writers West considered the condition to be caused by tearing of the tendon of the extensor origin from the external epicondyle with resulting periostitis. Higgs concluded that secondary infection, perhaps from infected foci, is present in damaged tissue. Perhaps the condition represents a variety of separate entities.

Conservative treatment was recommended[441, 713] for early acute cases: rest, heat, the arm in a sling or immobilized in a suitable splint. Massage and motion make the condition worse. Many patients recover spontaneously. If the condition becomes chronic most patients can be cured, according to West and North, by one manipulation under anesthesia after the method of Mills (1928): full flexion of the wrist with full pronation of the forearm, the elbow then being brought into full extension. West found the method of Cyriax[3] generally unsuccessful. If manipulation is not accepted, the application of a cock-up splint for a month may be required. Strapping gives tardy relief; prolonged rest of the part is not acceptable to most victims. Higgs favored the frequent use of a surgical procedure which North considered rarely necessary, one to be reserved for the most stubborn cases.

"The Obstetrical Shoulder." During delivery the shoulder joints of infants are subjected to considerable obstetrical trauma which may produce simple distortion, fracture of a clavicle or, more often, an epiphyseal separation of the upper end of the humerus. Scaglietti described the successive clinical and roentgenologic features in 53 cases of the last condition, which

may produce a characteristic rigidity of the shoulder joint with lateral displacement and retroversion of the epiphysis.

Treatment of Traumatic Arthritis: General Considerations. To hasten return of articular function in cases of traumatic arthritis, and to prevent as much residual disability and posttraumatic neurosis as possible, the application of physical therapy should not be left solely to the patient, but should be supervised carefully by physicians or technicians skilled in its use.[551] Simple methods of home physical therapy should be supplemented by suitable forms of professional physical therapy and occupational therapy. The special advantages of hydrotherapy in cases of traumatic arthritis were again stressed (Copeman). Lasher was disappointed in the effects of heat on many posttraumatic articular effusions. Measurements of articular effusions two or three hours after local application of heat often indicated slight increases, rather than reductions, in articular size. Hence he favored early aspiration of effusions. Truslow described a simplified compression bandage for traumatized joints with or without effusion. One layer of an Ace bandage is applied, e.g., to the knee. Then two pieces of sponge rubber, each about 8 inches long and 2½ inches wide with a small crescent cut out to fit the sides of the patella, are placed one on each side of the patella. The application of the Ace bandage is then continued until the rubber is entirely enclosed. Tarsy advocated more frequent use of periarticular and intra-articular injections of local anesthetics to relieve pain in traumatic and other types of arthritis. Aqueous solutions of 1 or 2 per cent procaine hydrochloride were generally used. Intra-articular injections were sometimes superior to periarticular injections. Eucupine in oil was sometimes used periarticularly, but produced severe reactions when given intra-articularly. Although the duration of induced anesthesia was short, rather permanent relief was often noted.

[By such injections satisfactory results are not infrequently obtained in various types of arthritis.—Ed.]

A novel procedure was advocated by Waugh as a result of his studies on the pH of synovial fluid: the pH of normal synovial fluid is about 7.4, similar to that of blood. The pH of 20 traumatic effusions averaged 5.65 at 24 hours, 5.95 at 48 hours, 6.55 on the third day, and 7.7 on the seventh day after injury; in other words such effusions were acid for three days and then became alkaline. The acidity was thought to be due partly to the presence of lactic acid derived perhaps from local tissue—cell damage and degeneration. According to Waugh (1936) during the healing of a fracture the pH of the primary hematoma also becomes acid. Waugh reasoned that perhaps the acidity of such effusions is a physiologic response to trauma designed to excite local leukocytosis, mesoblastic proliferation and repair. Waugh attempted to imitate this reaction by treating 11 cases of traumatic and 5 cases of atrophic arthritis with intracapsular injections of a solution of procaine acidified to pH 5 with lactic acid. The formula of the solu-

tion (Bayer) to produce such an acidity was: novocaine—HCl 2.0 gm., NaCl 0.5 gm., N/5 lactic acid 0.2 c.c., water to 100 c.c. Amounts of the solution used were 2 c.c. for elbows and ankles, 4 c.c. for knees and shoulders. Patients were hospitalized for injections; the solution was injected "around as well as into the capsule" under strict asepsis, then the joint was moved to its full range in all directions, and the limb was immobilized in plaster for two weeks followed by the use of an Elastoplast support until function was regained. Although the 11 cases of traumatic arthritis so treated were "those of severe disablement which had resisted various forms of treatment" full functional recovery resulted in all.

[This work is very interesting but needs confirmation. Perhaps results were due, not to the injections, but to the measures used thereafter. Studies should be made on controls similarly treated except for the injections.—Ed.]

Synovectomy was performed by Inge in nine cases of "chronic proliferative synovitis traceable to chronic trauma, such as torn menisci or loose bodies." In all cases symptomatic and functional improvement resulted. Noting that Speed (1924) advocated synovectomy for traumatic arthritis, Swett stated: "It is gratifying to observe that complete recovery has been the rule in all of these cases thus far reported." He considered it logical to expect recovery after removal of chronically inflamed synovial tissue which has largely lost its function. Without reporting results of his own Swett concluded: "It may be confidently said that chronic traumatic arthritis provides one of the major indications for synovectomy."

[We believe that in general there should be a long minimal time limit to allow spontaneous healing before synovectomy. But under certain circumstances synovectomy may be indicated. In traumatic arthritis thickened synovia is the result not the cause of the trouble. If the underlying cause can be corrected surgically, then the thickened synovia can be removed at the same time with benefit, but if incongruity of articular surfaces is not corrected synovectomy cannot be expected to result in a permanent cure.—Ed.]

Gonorrheal Arthritis and Gonorrheal "Rheumatism"

Incidence. Despite efforts of national and civic bodies there is as yet no significant reduction in the incidence of gonorrhea in the United States. Reviewing the epidemiology of the disease, Vonderlehr and Usilton published the annual incidence of attacks of acute gonorrhea among white and negro males and females in 46 surveyed localities in the United States. The incidence per 1000 population varied from a maximum of 46.6 white males (Charleston, W. Va.), 69.9 negro males (Lincoln, Neb.), 15.1 white females (El Dorado, Ark.), and 46.5 negro females (Newton, Kan.) to a minimum of 2.3 white males (also Newton, Kan.), 6.6 negro males (Texarkana, Ark.), 0.2 white females (rural Nebraska), and 2.2 negro females (Omaha, Neb.). The European incidence of the disease also has not been reduced significantly (Fessler). The disease is not incurable, but the careless, inadequate attitude of the public, including patients and physicians, has so far been largely incurable.

[The incidence of gonorrheal arthritis was accepted [139] as being from 2 to 3 per cent of patients with gonorrhea. This incidence seems high to one of us (M. H. D.). —Ed.]

The patient's occupation may largely determine the site of his gonorrheal arthritis (Rorke). Most commonly affected are hands and wrists among manual workers, knees, feet or ankles among those who stand or walk a lot—waitresses, clerks, salesmen. Rorke concluded that severity of climate was also a factor in the incidence.

Clinical Data. Among 58 cases of gonorrheal arthritis seen by Burbacker and Weiland the ratio of monarthritis to polyarthritis was about 2:3. The site of involvement in order of frequency was knee, metatarsus, ankle, metacarpus, wrist, hip, elbow, sacro-iliac, shoulder, sternoclavicular and temporomandibular articulation. Infections of the knee constituted 44 per cent of the total joints affected.

Recent reports have emphasized the frequency and diagnostic significance of certain skin manifestations which may accompany gonorrhea and gonorrheal arthritis. According to Buscke (1912) gonococcal eruptions are of four main types: (1) erythemas, (2) urticarial and nodose lesions, (3) hemorrhagic and bullous lesions, (4) hyperkeratosis. Lesions recently described in cases of gonorrheal arthritis were erythema nodosum,[4] petechiae and small red sore spots associated sometimes with a central white necrotic area, at other times with vesiculation and seropurulent fluid.[5] Showers of petechiae, some with white centers, appeared in Lichtman's fatal case of gonococcal endocarditis with jaundice; no pelvic focus was found. Keil reported five cases of gonorrheal arthritis, gonococcemia and distinctive hemorrhagic vesiculopustular and bullous skin lesions. Although a history of old gonorrhea was generally obtained, in none of the five cases was an active local gonococcal focus found. Because the acute febrile polyarthritis sometimes followed acute sore throat and especially since cardiac murmurs were present in two cases, diagnoses of rheumatic fever were entertained. However, gonococci were isolated (by smears, cultures or both) from blood, joints or skin lesions. [The fact that a sore throat or a respiratory infection often precedes acute gonorrheal arthritis has been noted by Schottmüller, 1921, Wheeler and Cornell, 1930, and Keefer and Spink, 1937.—Ed.] The five patients were young adults, profoundly ill, with a somewhat remittent but very irregular, atypical fever. In four cases gonococcal complement fixation tests on blood gave negative results; perhaps the method used was not sensitive enough. Despite the presence of cardiac (soft systolic apical) murmurs and the proved bacteremia, gonococcal endocarditis was apparently absent, as the murmurs disappeared and the patients recovered. The metastatic dermatosis present was "distinctive" and presumably caused by a hematogenous dissemination of gonococci rather than by toxemia. The typical eruption generally appeared during the febrile period, and tended to occur in crops; sometimes only one crop appeared. Generally only a few (1 to 8) lesions were present; occasionally they were distributed over the entire body.

They were usually discrete, rarely coalescent. They generally affected extremities, occasionally trunk, face, scalp. They appeared first as erythematous macules which speedily acquired a central vesicle or pustule. Hemorrhages typically occurred in the center of the lesion; often the exudation of fluid and cells caused bullous formation. "The classical lesion in full development is a hemorrhagic, purulent vesicle or bulla, surrounded by a more or less broad erythematous areola." The hemorrhagic feature may be absent. Keil discussed the differentiation of these lesions from the "rheumatic" and other dermatoses.

[Three of us (W. B., M. H. D., and P. S. H.) have recently seen four cases with similar skin lesions and with gonorrheal arthritis proved by articular culture; diagnoses were at first difficult because no active local lesion was found. Those concerned with diseases of joints should familiarize themselves with this skin lesion. In such cases efforts should be made to confirm the diagnosis by making cultures from the skin lesions and from blood.—Ed.]

Difficulties which may arise in diagnosing gonorrheal arthritis were illustrated in the cases of Reitzel and Kohl: in 14 of 25 cases of proved gonorrheal arthritis the history did not indicate previous gonococcic infection and either routine smears were "negative" or no urethral or cervical discharge was present. Diagnoses were made by recovering gonococci from blood (7 cases), synovial fluid (16 cases) or both (2 cases). Four patients had gonorrheal arthritis, gonococcemia and cutaneous eruptions such as those noted by Keil. Five patients had gonococcemia, arthritis and gonococcic endocarditis, the last being confirmed at necropsy in three cases. In one case of endocarditis a maculopapular eruption later became pustular, leaving necrotic centers and bullae from which gonococci were recovered. This contradicts the view of Keil that such eruptions do not occur in cases of gonococcal endocarditis.

[In our four cases of this skin lesion endocarditis did not develop.—Ed.]

Pathology: Roentgenograms. No new studies thereon were reported.

Laboratory Data: 1. Identification of Gonococci in Smears. Only an approved Gram-stain technic should be used to identify gonococci in "spreads" (smears).[535] The use of methylene blue and other short-cut stains leads to frequent errors. Gonococci may be particularly difficult to identify in smears from patients who have already taken sulfanilamide. In such cases the technic must be very exact.

2. Cultures of Gonococci. Accumulating evidence indicates that gonococci can be recovered by culture in about twice as many cases as by smears. Ch'in obtained positive cultures from urine as often as from prostatic or urethral discharges. Since gonococci are viable in urinary sediment for 20 to 43 hours specimens could be sent fairly long distances for culture. New culture methods were proposed. Beck described a new chocolate agar; beef blood was used. A higher percentage of positive results and excellent growths of even weakly growing strains were obtained. For collecting material for cultures Greene and Breazeale advocated the use of swabs impregnated with sterile ascitic fluid. Reitzel and Kohl used hormone-brain broth or a brain-heart infusion with sterile ascitic fluid for culturing gonococci. The use of 8 per cent carbon dioxide did not seem essential to the successful recovery of gonococci.

3. Gonococcal Complement Fixation Test. This test was first used by Muller and Oppenheim (1902) as an aid in differentiating gonorrheal arthritis from other arthritides. Many physicians regard the test very highly; others consider it of limited value because of difficulties in its performance and interpretation. Results of the test are influenced by several factors as noted in previous Reviews and as again discussed by several authors.[52, 490, 775, 1016] From their studies on 760 patients Jacoby, Wishengrad and Koopman concluded that the test as generally performed is of limited usefulness and needs further refinement and standardization. Price made tests on 545 patients with untreated gonorrhea: according to him a positive result may be expected during the first week of the disease in 27 per cent of cases, during the second week in 46 per cent, during the third week in 70 per cent, during the fourth week in 88 per cent and during the fifth and sixth weeks in 100 per cent of cases. Location and anatomic spread of the disease notably influence the positivity of the test. After injections of gonococcal vaccines have been given to rabbits or nongonorrheal persons for four days results of the tests will be positive, will become very positive after 10 days of injections and negative six weeks after the injections are stopped. Price obtained positive tests in 80 to 90 per cent of cases of gonococcal arthritis, rheumatism or tenosynovitis.

Using this test as an index to the relative value of sulfonamide compounds Price concluded that prontosil album (sulfanilamide) prevented the appearance of a positive test more effectively than uleron. Weiss and Arnold advised use of larger quantities of patient's serum than are generally used: thereby the sensitivity and stability of the test were notably enhanced without increasing the number of nonspecific and anticomplementary reactions.

[More data on incidence of false positive tests in persons without gonorrhea are needed. —Ed.]

Comparative Value of Smears, Cultures and Complement Fixation Tests. From a study of 100 women with chronic gonorrhea Jacobsen, Mason and Arnold concluded that in such cases cultures are superior to direct smears, and fixation tests are superior to either cultures or smears. Urethral smears were "positive" in only 3 per cent, "doubtful" in 16 per cent, "negative" in 81 per cent. Cervical smears were positive in 4 per cent, doubtful in 16 per cent, negative in 80 per cent. Cultures from urethra were positive in 13 per cent, from cervix in 17 per cent. Gonococcal complement fixation tests were positive in 32 per cent. Of the 100 cases "10 were positive by bacteriology and serology, 12 positive only by bacteriological methods, and 21 positive only by the complement fixation test."

The comparative value of cultures (modified McLeod method) and smears on 245 adult female patients was studied by Carpenter, Leahy and Wilson. The cultural method was found to be 191 per cent superior to the smear method. However, in 8 per cent of cases cultures were negative but smears were positive. Therefore, both tests should be used whenever possible. The combination of both tests was 208 per cent superior to the smear method alone. Stout and Todd also noted the superiority of cultures over smears.

These laboratory tests are therefore of considerable value in confirming the clinical diagnosis of gonorrhea and gonorrheal arthritis. But when laboratory tests are negative in the presence of clinical data highly suggestive of gonorrhea full significance should be given the latter, and therapeutic tests should be promptly instituted regardless of negative laboratory tests.[535]

4. Tests of Bactericidal Power of Blood and Synovial Fluid. Spink and Keefer [518, 897] continued their studies [5] on the bactericidal power of blood and synovial fluid for gonococci. In some cases of gonorrheal arthritis no gonococci can be recovered from synovial fluid; in these the prognosis for articular recovery is better than in cases in which gonococci are present in synovial fluid. Several factors operate to allow or prevent infection of the synovial cavity. One of them is the degree of

inflammation present: if the inflammation in subsynovial and synovial tissues is severe enough to destroy parts of the membrane, bacteria gain access to synovial fluid. Other factors are the number of infecting organisms and the antibody response. During gonorrhea specific antigonococcal antibodies develop, become present in blood, and diffuse into synovial fluid. Sometimes the concentration of antibodies in synovial fluid is equal to that in blood; at other times it is less. According to Spink and Keefer gonococci are first "sensitized" by antibody and then their destruction is completed by complement. When the antibody titer of both blood and synovial fluid is high, gonococci that reach the articular cavity are killed, and synovial fluid is kept sterile. When the antibody titer of blood, and consequently of synovial fluid, is low, gonococci will survive in synovial fluid. In some cases the antibody titer of synovial fluid is low and the fluid is therefore not bactericidal, even though the blood possesses a high antibody titer and is actively bactericidal. Since gonococci seem to thrive in regions supplied by large amounts of mucus (urethra, vagina, conjunctivae, joints, tendon sheaths) Keefer and Spink suggested that mucin either favors the growth of gonococci or somehow prevents their destruction by tissue antibodies. They studied the effect of adding mucin to whole blood of patients with gonorrheal arthritis, normal persons and rabbits. The addition of mucin to defibrinated blood depressed the bacteriolytic titer of the blood for gonococci. These results suggest that synovial mucin does not lower the amount of complement in synovial fluid or interfere with the action of complement. But apparently in some way as yet not clearly understood, mucin protects gonococci from the action of antibody unless a large amount of antibody is present.

[One of us, W. B., has observed that the blood from nongonorrheal patients may show the same variations in bacterial killing power to various gonococcal strains as do patients with acute or chronic gonorrhea, with or without complications. Repeated examinations at regular intervals for as long as six months failed to reveal any increase in the bacterial killing power.—Ed.]

5. Concentration of Vitamin C in Blood. While comparing the concentration of vitamin C in the blood of patients with atrophic arthritis to that of normal persons and other controls Rinehart and his colleagues obtained low values for vitamin C in plasma in 13 cases of gonorrheal arthritis. Normal values ranged from 0.22 to 1.45 mg. per 100 c.c. of plasma and averaged 0.7 mg. The plasma values for vitamin C among gonorrheal patients ranged from 0.09 to 0.64 mg. (average 0.22 mg.), indicating a definite vitamin C deficiency. Perhaps this deficiency was the result of the infection, for infection depletes the organic reserve of vitamin C. Another suggestion was offered: perhaps the vitamin deficiency was primary, and lowered the resistance of joints to subsequent bacterial invasion.

[Concentrations of vitamin C in blood are low in most patients with any debilitating disease.—Ed.]

Treatment of Gonorrheal Arthritis

The two most effective methods of treating gonorrheal arthritis continue to be fever therapy and sulfanilamide, either used alone or in combination. Although use of sulfanilamide or related compounds has largely supplanted use of fever therapy, certain cases of gonorrhea and gonorrheal arthritis are resistant to sulfanilamide, and hence are still suitable for fever therapy. Therefore it seems important to review current papers on fever therapy reporting work chiefly done before the use of sulfanilamide became general.

Fever Therapy for Gonorrheal Arthritis

Eleven papers reported the results of fever therapy in about 560 cases of gonorrheal arthritis. Bauer and Cecil treated 71 cases: (24 acute, 39 subacute, 8 chronic). Complete symptomatic relief was noted in 12 acute, 18 subacute and 2 chronic cases; 10 acute, 12 subacute and 4 chronic cases were greatly improved. The rest were not benefited significantly. Results in Bierman and Levenson's 40 cases were "satisfactory and frequently dramatic"; in 32 "cure" was effected but in 9 physical therapy was needed to restore normal articular motion; in 8 improvement occurred but these were classed as failures because genital cultures remained positive. Among 40 cases of pelvic gonorrhea treated by Darling, Berris and Newman were 5 cases of gonorrheal arthritis. Results of fever therapy in the arthritic cases were not given separately, but of the 40 patients a total of 82 per cent were cured; 3 with one fever session, 25 with 2 sessions, 5 with 3 to 8 sessions. Seven patients (18 per cent) were unable or unwilling to continue treatment until cured.

Egan and Piaskoski treated 29 acute and 6 chronic cases of gonorrheal arthritis. Of the patients with acute gonorrheal arthritis 25 (86 per cent) were "completely relieved" by one to three fever sessions of 4 to 5 hours each at 106 to 107° F. Of the 4 patients not cured, 3 were "improved," one was slightly improved. In the 6 chronic cases duration of the disease was "from two months to many years"; none of the patients was cured; only 3 were improved. Sixteen patients with gonorrheal arthritis (stage unstated) were given hyperpyrexia by Gurnee: all were "uniformly benefited, being listed on discharge as 90 to 95 per cent improved." Only one fever session was required in 8 cases, two sessions in the rest. Combined general and pelvic heating was used. Of Owens' 30 patients 70 per cent were "cured," the rest "improved."

Purcell treated 2 acute cases: after one treatment relief was complete in one case, marked in the other. Of Schmidt's 7 patients, 6 were "promptly improved." Solomon and Stecher reviewed their results in 103 cases (84 acute cases, i.e., less than 8 weeks in duration and 19 chronic cases in which articular symptoms had lasted for months to seven years). [We do not believe that provable cases of gonorrheal arthritis remain active for more than a few weeks, certainly not for years, although residual deformity and stiffness may remain for years.—Ed.] Relief was complete in 52 per cent, partial in 30 per cent, insignificant in 18 per cent. Failures were often due to the patient's unwillingness to continue treatments. The average duration of the arthritis of patients completely relieved was 7.2 weeks, of those partially relieved, 11.7 weeks, of the rest 9.6 weeks.

Excellent results were also noted by Trautman, Stroupe and Devlin who treated 61 cases (37 acute, 24 chronic). Complete recovery or marked improvement was noted in 84 per cent of the acute and in 54 per cent of the chronic cases. Associated genital infections were cured thereby in 86 per cent of the acute and in 75 per cent of the chronic cases. In the acute cases

all of the patients who were not cured were moderately improved. Of the other 11 chronic cases 6 patients were moderately improved, 5 were slightly improved or not benefited. For all these cases an average of 7 to 8 fever sessions (each 5 hours at 106 to 107° F.) was required, a greater number than prescribed by many workers.

The true value of fever therapy in gonorrheal arthritis has been difficult to assess because some patients tend to recover spontaneously and rather rapidly, and because most workers have not compared their results from fever with those from less strenuous methods. Hence the second report of Schnabel and Fetter [5, 839] with controls is of special interest. Cures were obtained in 68 per cent of 70 acute cases treated with fever therapy but in only 6 per cent of 70 acute cases treated otherwise (old methods: local chemotherapy and physical therapy). The average period of hospitalization for treatment was 21 days in the first group, 39 days in the second. Cures were also obtained in 26 per cent of 23 chronic cases treated by fever but in only 4 per cent of 23 chronic cases treated otherwise. The average period of hospitalization for treatment was 33 days for patients given fever, 143 days in those treated otherwise. These statistics certainly indicate the superiority of fever therapy over older methods.

Summary. These reports present further evidence that complete cures are obtained in 70 to 90 per cent of acute cases and in about 60 to 80 per cent of chronic cases of gonorrheal arthritis in which from two to four (occasionally six or eight) fever sessions are used. The fever sessions almost uniformly consisted of five or six, occasionally seven, hours at 106 to 107° F. (rectal) given every two to four days.

[Fever therapy can only arrest the active disease; it cannot restore tissues already damaged, therefore it should be used early if at all.—Ed.]

Fever Therapy for Nonarticular Gonorrhea

In the arthritic cases mentioned fever therapy generally controlled the genitourinary infection also. In some cases genital cultures or smears remained positive after articular symptoms disappeared, and two or more extra fever sessions were required. Occasionally fever therapy failed to cure the genital infection even though it cured the arthritis. In addition to the reports noted several other papers summarized the results of fever therapy for nonarticular gonorrhea.

Bierman and Levenson and Bierman and Horowitz treated 165 cases of gonorrhea. Of 125 women 93 per cent became free of gonococci after an average of 1.9 fever sessions (each 10 to 12 hours; combined general and pelvic heating). Of 40 males 70 per cent became free of gonococci after an average of 2.8 treatments. Failures were due to inadequate heating, or occasionally to the heat resistance of certain strains. As a result of their experiences with 95 cases of acute and chronic gonorrhea Egan and Piaskoski stated that " fever therapy will quickly and permanently cure gonorrhea and its complications in over 90 per cent of patients who are willing and able to undergo adequate treatment." [However, about 10 to 20 per cent of patients will not accept a full series of fever sessions.—Ed.] Of Gurnee's 79 cases of acute genital gonorrhea treated by a combination of hot box and Elliott treatments 84 per cent were cured by one or two fever sessions. Of 150 women with pelvic gonorrhea to whom Horowitz gave combined pelvic diathermy and systemic fever therapy, 92

per cent were freed of gonococci. When Horowitz had perfected the technic by which his last 73 cases were treated, over 60 per cent required only one treatment.

Krusen and his colleagues [554, 556, 789] favored the use of one 10 hour session of fever combined with pelvic diathermy instead of the usual successive short fever sessions. At times more than one session was required. Of patients with positive cultures, 95 per cent were cured after one or more sessions of fever. In 76 per cent of 95 cases treated by a single 10 hour session cultures became negative.[554] Of 266 patients studied by Krusen, Randall and Stuhler and given one to 13 sessions of fever (each 5 to 12 hours at 106.7° F.) 246 (93 per cent) obtained negative cultures and all were clinically improved. In another series of 31 cases given a single 10 hour session of general fever combined with additional pelvic heating (vaginal diathermy or Elliott method) 94 per cent gave consistently negative genital cultures after a single 10 hour fever session.[789] Excellent results from fever therapy in various types of genital and pelvic gonorrhea were also reported by Davis, R. Kovacs, Owens, Paul, Purcell, Schnabel and Fetter and by Trautman, Stroupe and Devlin.

Fever Therapy for Special Complications of Gonorrhea

1. Gonococcal Endocarditis. This is generally fatal. There are 139 cases reported in the literature; in the 108 "proved cases" collected by Freund, Anderson and Lilly the mortality was 94 per cent. The clinical and diagnostic features of the 7 recovered cases of gonococcal endocarditis were summarized. Freund, Anderson and Lilly reported an additional case in which fever therapy resulted in cure. A negress, aged 20 years, had gonococcemia and cardiac findings consistent with a diagnosis of acute endocarditis. The patient was given six fever sessions totalling 30 hours at 106 to 107.4° F. Fever, acute arthritis and cardiac abnormalities disappeared; cervical smears became negative and remained so four months thereafter.

[There is no certain method of diagnosing gonococcal endocarditis during life. Some "cured cases" may have been cases of gonococcal bacteremia without true gonococcal endocarditis.—Ed.]

2. Gonorrheal Arthritis Complicating Pregnancy. Acute gonorrheal arthritis occasionally complicates pregnancy. Upton, who reviewed the subject, considered fever therapy dangerous in such cases "since the products of conception always suffer, and death of the fetus may occur." However, Gurnee treated two cases of gonorrhea complicated by early pregnancy by combined pelvic and general hyperthermia. Each patient required three treatments. Neither patient aborted. One was cured, the other was not.

[How were the babies?—Ed.]

General Remarks on Fever Therapy

Preferred Methods. Several workers [336, 839, 889, 962] preferred to give several short (5 to 7 hour) sessions with a Kettering Hypertherm. Zeiter used an unnamed heated humidified cabinet. Inductothermy seemed preferable to Castleden, and Heald. According to Phillips forms of penetrating heat (e.g., short wave electromagnetic induction) are physiologically superior to radiant heat. Osborne and Markson preferred the use of high frequency currents as safer and more comfortable than external heat; the former produces less alkalosis, a slower pulse, and preserves the natural heat gradient of the body which external heat does not. Schmidt preferred a cabinet equipped with vaporized hot water at a temperature of 130° F. arranged so that a cold spray could be applied at any time to cool the skin. The superiority of the combined technic (general fever plus additional pelvic heating) was upheld by several. For pelvic heating Gurnee favored the Elliott method; Bierman and Levenson, Horowitz, and Krusen and his colleagues preferred vaginal diathermy as being easier to

give and more comfortable for patients. Horowitz, and Krusen and his colleagues favored the use of one or two fairly long (10 to 12 hour) sessions of general fever, with pelvic heating to 109 to 112° F. (rectal). Krusen and his colleagues produced general fevers to 106.7° F. but Horowitz considered that a temperature of 105.5 to 106° was sufficient in view of the added local heat, and considerably easier and safer for the patient. The use of "low fever" (1° F. less than usual) supplemented by the inhalation of 50 to 80 per cent oxygen was found to be less effective than the usual amounts of fever (Krusen, Randall and Stuhler). The latter seemed to be slightly more effective when combined with oxygen therapy but results were not sufficiently better to continue the additional procedure. Darling, Berris and Newman found it inadvisable to combine local pelvic heating and systemic hyperpyrexia, because of their inability to gauge patients' temperatures accurately. Mouth temperatures were inaccurate because iced saline solution was constantly given; rectal temperatures do not indicate the amount of general fever. Randall, Krusen and Bannick recommended the following special preliminary preparation: the patient's skin is exposed to an ultraviolet lamp until a mild erythema is produced, then he is immersed in the Hubbard tank for 30 minutes, then wrapped in blankets for 1½ hours prior to the fever session. "The vasodilation thus secured aids the patient in tolerating the prolonged fever treatment." The intravenous injection of 5 per cent solution of dextrose in physiologic saline solution just after treatment was also considered desirable. Elkins described the arrangements and equipment required for a good fever therapy department.

Carpenter, Boak and Warren again stated their belief that the most rational method was to determine the thermal death time of each patient's gonococci and give one long (8 to 24 hour) fever session at 41.5° C. The thermal death time of 250 strains of gonococci recovered from various tissues varied from 6 to 34 hours at 41.5° C., but was between 11 and 21 hours for 75 per cent of the strains. No correlation was found between the thermal death time of the gonococcus and either the site of infection or severity of symptoms (virulence of invading strain).

[Few physicians have the facilities for rapidly determining the thermal death time of individual strains, and few patients are willing to endure such long sessions. The use of one or two 10 hour sessions seems to be a successful compromise.—Ed.]

Physiologic Effects. These effects were similar to those given in previous Reviews.[405, 546, 790, 837, 885, 886] Reactions indicating impending vascular collapse and shock were described.[888] Also reported were studies on the acid base balance,[237] and on the changes in blood volume and water balance which indicated the need of giving plenty of fluid during fever therapy to avoid shock.[361] Additional studies reported at the First International Conference on Fever Therapy (1937) were reviewed.[552] Studying psychologic and psychiatric reactions to fever therapy Ebaugh, Barnacle and Ewalt noted an exaggeration of patients' outstanding personality patterns. Phlegmatic patients were unperturbed and coöperative; aggressive persons became more aggressive and restless; contented sociable persons became elated and even euphoric during hyperpyrexia; pessimists exhibited deepened dissatisfaction with everything in general, and hypochondriacs were greatly concerned with their physical state. Emotional conflicts associated with certain diseases played a rôle in the patients' reactions to the treatments. Patients with gonorrhea commonly exhibited anxiety, fear and depression. Some patients with chronic arthritis, long sufferers with pain and invalidism, exhibited depression and hypochondriasis; others, however, appeared composed, congenial and even elated. Choreic children were emotionally unstable but were not anxious or apprehensive. Delirium was studied as it appeared in 350 patients during fever therapy: 390 episodes of delirium occurred; 104 gonorrheal patients had 170 such episodes, 35 patients with atrophic arthritis had 17, and 45 choreic patients had 12; the rest occurred in other cases. Episodes of delirium were materially reduced by psychotherapy, by increased experience with hyperpyrexia, and particularly by limitation of sedatives.

Complications and Untoward Results. Current statistics indicate again that when fever therapy is given in a hospital by a trained personnel it is essentially safe. Among 620 patients given over 2600 fever sessions at The Mayo Clinic there has been only one fatality.[556] Trautman, Stroupe and Devlin noted only one death (no details given) among 430 patients given 2597 treatments, but reported a few other untoward reactions: cardiovascular collapse in three cases, burns in one case, severe abdominal pain after treatment in one case, and an attack of grand mal after treatment of an epileptic. Kovacs reported no fatalities during 500 treatments given to an unstated number of patients. Friedman and Stettheimer reported the case of a child aged 2½ years with resistant acute gonorrheal vaginitis who died nine hours after the first and apparently well tolerated treatment (inductothermy; 8 hours at 106.6° F.). This death, the only one so far reported among children, resulted from circulatory failure and exhaustion of the heat regulating mechanism. They also noted (no details) the death of an elderly man with gonorrheal urethritis after hyperpyrexia. A choreic child given hyperpyrexia in a hot bath (2 to 3 hours in water at 120° F.) became unconscious and had convulsions; thereafter Lowenburg advised hot water temperatures at 105°, certainly not over 110° F. Gurnee disapproved of raising rectal temperatures to 106.7° F.: as a result of such treatments one patient died of heat stroke and two others had severe heat strokes with burns necessitating skin grafting. Since he adopted the combined heating method with mouth temperatures at 105° F. and vaginal temperatures at 115° (Elliott method) he noted no significant reactions except occasional mild vaginal bleeding. Gurnee abandoned the use of short-wave therapy to induce local pelvic heating because it produced some deep vaginal burns and vesicovaginal fistulas necessitating surgical repair; these did not occur with the Elliott method.

To prevent untoward reactions one must recognize signs of impending collapse (sudden increase in pulse rate; a rate about 160 or more; a sudden decrease of systolic blood pressure to 60 or 70 with an increase in diastolic pressure). To treat shock from fever therapy Solomon and Kopp removed patients from the fever cabinet, gave intravenous infusions of glucose 5 per cent and normal saline solutions, and gave inhalations of 5 to 7 per cent carbon dioxide in oxygen if respiratory embarrassment or tetany occurred.

Conclusions on the Merits of Fever Therapy for Gonorrhea and Gonorrheal Arthritis

Because of the excellent results obtained, fever therapy was considered "virtually a specific for gonorrheal arthritis,"[270] and, "the quickest and most dependable method of curing gonorrhea."[743] At a round-table conference[535] of 23 genito-urinary specialists the consensus was that "properly used, fever therapy is probably the most effective form of therapy for gonococcal infections, but the cost of treatment and the limited number of hos-

pitals where the technic is safely and effectively used constitute its greatest limitation." One critic queried: "Is it logical to submit an average case to this severe treatment? Must we use a cannon to bring down a duck? The punishment of fever therapy in the male does not seem to fit the crime" (Strachstein). Others, however, regarded the misery which gonorrhea produces as "no small game" and considered fever therapy justified for patients who do not respond to the newer forms of chemotherapy. Nevertheless, although conceding the effectiveness of fever therapy, they criticized it as a time consuming, uncomfortable, generally strenuous and occasionally serious ordeal which, being a hospital procedure necessitating special attendants and the use of costly apparatus, is available only to a small percentage of patients. And of those who accept it from 8 to 30 per cent are unable,[743] unwilling or "too frightened" [962] to accept adequate amounts.

Sulfanilamide: General Considerations

Introduction. Before discussing the use of sulfanilamide for gonorrhea and gonorrheal arthritis we will discuss the general topic of sulfanilamide and the newer concepts regarding it. The literature on sulfanilamide and related compounds has become voluminous indeed. From the publication of the first clinical report on the use of prontosil (Domagk, Feb. 15, 1935) until Nov. 1, 1937, 215 articles on sulfonamide compounds appeared.[840] The most significant of these were reported in our last Review.[5]

In addition to our synopsis which stressed clinical features, a number of short general reviews on sulfanilamide appeared during 1938.[27, 68, 121, 128, 319, 390, 498, 515, 573, 688, 817, 852, 902, 1000] Six reviews deserve special mention. Schulte reviewed concisely the early chemical and experimental work on the sulfonamide compounds. In five other reviews also ideas on the mode of action of these drugs, their toxicity, optimal dosage, clinical results, etc. were considered. That of Holman and Duff was the most comprehensive and contained 162 references to the literature of 1934 to 1937. McGinty considered all phases of sulfanilamide toxicity, and noted 164 references, mostly of 1937. Schnitker's review concerned 69 references to the literature of 1935 to 1937. Two excellent synopses included considerable material published in 1938: Garrod reviewed 166 reports (1934 et seq.) of which about 75 appeared in 1938, and Whitby reviewed 182 articles (1935 et seq.) about 100 of which appeared in 1938. Students of the subject can find the references to practically every significant report on the entire subject in these six useful reviews.

[Two recent books also review the entire subject: one by Long and Bliss, 1939, and one by Mellon, Gross and Cooper, 1938.—Ed.]

During 1938 several hundred papers on sulfonamide compounds appeared; we have reviewed herein only about 200 which seemed of special interest to physicians concerned with the use of these drugs to combat or prevent diseases of joints.

Terminology. Fortunately the approved terminology for these various drugs has been widely accepted, and the literature of 1938 spoke almost exclusively of sulfanilamide and not of its various synonyms (prontosil album, prontylin, etc.).[5]

Mode of Action. It is not yet known exactly how sulfanilamide acts against infection; hence its use is still largely empiric. The following modes of action have been suggested:

1. Sulfanilamide has a direct bactericidal effect on certain bacteria in vivo even though not in vitro. This idea suggested by certain earlier workers is still upheld by some current writers. When enough sulfanilamide was given, Farrell, Lyman and Youman found urine and prostatic secretions to be bactericidal to certain organisms (colon bacilli, *Staphylococcus aureus*); against these infections at least the drug acts directly in the urinary tract. A different view was held by Vest, Hill, Harrill and Pitts who frequently noted failures and successes in patients with equally high concentrations of sulfanilamide in blood and urine. They also noted marked reduction of urethral gonococci before there was much, sometimes even before there was any, sulfanilamide in urine. Hence they concluded that the drug acts on infections of the urinary tract through the blood stream and not solely in urine. Long (1937) did not believe the effect of the drug was primarily bactericidal. He and more recently others [199, 350] have noted no strong bactericidal effect of sulfanilamide in vitro or in vivo except perhaps in urines possessing high concentrations of the drug. However, Keefer and Rantz noted that the blood of gonorrheal patients receiving sulfanilamide, or normal blood to which the drug was added possessed bactericidal properties against gonococci. Studying the effect of the drug on various strains of gonococci, Cohn and Cohn and Peizer noted no bactericidal effect of sulfanilamide when gonococci were suspended in physiologic saline solution and injected intraperitoneally into mice, but they noted definite protection for mice infected with a gonococcus-mucin suspension.

2. Sulfanilamide possesses a bacteriostatic action on certain bacteria in vivo and in vitro. Most investigators agree that the drug somehow arrests bacterial growth, but are not agreed as to whether the action on bacteria is direct or indirect. Some workers believe that as a result of the bacteriostatic action of the drug, the rate of multiplication of bacteria is reduced; the bacteria cannot produce enough leukocidin and other bacterial toxins to inhibit phagocytosis by the leukocytes (Cokkinis and McElligott, Gay). But Britton was unable to demonstrate either bacteriolysis or bacteriostasis in vitro with sulfanilamide, proseptasine, soluseptasine, T 607 and T 626.

3. Sulfanilamide hinders capsule formation of bacteria. This idea is disputed.

4. Sulfanilamide activates the reticulo-endothelial system. This idea is also disputed.[350]

5. Sulfanilamide stimulates phagocytosis. A number of current investigators found no evidence to support this idea.[205, 736, 737, 887, 989]

6. Sulfanilamide aids phagocytosis indirectly; bacteria are "sickened" by the drug and rendered more susceptible to normal phagocytosis. Kolmer and his associates gave the drug to rabbits experimentally infected with beta hemolytic streptococci so that skin, blood and joints were infected. The drug usually increased phagocytosis of streptococci in local cutaneous lesions; hence it was concluded that its effectiveness depends in part on its ability to promote phagocytosis by inhibiting the growth and toxin-production of bacteria. Phagocytosis is a helpful but not essential factor (Lockwood).

7. Sulfanilamide activates opsonins. Finkelstein and Birkeland regarded the presence of serum essential for the drug to be effective in causing phagocytosis in vitro; "the serum-sulfanilamide complex acts as an opsonin to enhance phagocytosis." But Reimann saw no reason to confuse matters by introducing the word opsonin. Obviously when any drug inhibits bacterial growth, some of the bacteria will die and be taken in by phagocytes.

8. Sulfanilamide has a certain immunizing or detoxifying effect; it may neutralize such toxins as hemolysins and leukocidins. From their experimental work on

mice Carpenter, Hawley and Barbour concluded that sulfanilamide inactivates "gonococcal toxin." They noted that certain gonorrheal patients recovered with minimal concentrations of sulfanilamide in blood; others failed to respond to maximal concentrations; still others lost their symptoms but still retained viable gonococci. These facts suggested that the drug acts on bacterial toxins, not on bacteria themselves. Others noted no antitoxic effect from sulfanilamide.[199, 479, 517, 527, 591] It does not stimulate antibacterial immunity, does not neutralize streptococcal toxins (hemolysin, fibrinolysin, dermatoxin), does not affect the formation of antifibrinolysins, and does not prevent or delay the production of gonococcal complement-fixing antibodies.

9. Sulfanilamide inhibits the production of bacterial toxins. This view, held earlier by Long (1937), is supported by Cokkinis and McElligott and by Gay. According to Snowden and Ball the drug "controls gonotoxin." However, Gross, Cooper and Lewis, and Huntingdon reported that the drug does not significantly inhibit the formation of streptococcic hemolysin or fibrinolysin and does not affect the formation of toxins in vitro. If a drug inhibits bacterial multiplication it will naturally inhibit toxin production to a certain degree. Gay noted a decrease in the production, not of fibrinolysin or leukocidin, but apparently of hemotoxin. Hence to a limited extent sulfanilamide does inhibit the production of some bacterial toxins. According to Gay this inhibition permits certain defense cells, especially macrophages, to accumulate from the circulation and from local sources, and destroy the inhibited bacteria more readily.

10. Sulfanilamide operates by an electrophysical action: Green's hypothesis, unsupported by experimental data, is that sulfanilamide, like Congo red, may be effective because, carrying a negative electric charge, it neutralizes the bacteria carrying a positive charge.

11. That sulfanilamide causes bacterial "starvation" was advanced currently.[346, 589-591] The action of sulfanilamide is a delayed one, for a while after it is given bacteria actually multiply, according to Garrod; only later does bacteriostasis become evident. This suggested that the drug somehow interferes with assimilation of food by bacteria. Lockwood and his colleagues reported that when the drug was added to human serum, the serum became bacteriostatic for hemolytic streptococci. This bacteriostatic action could be prevented by adding small amounts of peptone. This suggested that the drug interferes with the ability of virulent hemolytic streptococci to use serum or tissue protein as food from which to obtain nitrogen. Without the latter the bacteria cannot multiply.

Comment. Arguments for and against these ideas were reviewed by several writers.[27, 46, 319, 346, 461, 589, 798, 1027] Obviously the mode of action of sulfanilamide is still uncertain. The controversy still revolves around the question whether under certain conditions sulfanilamide is bactericidal as well as bacteriostatic, whether phagocytosis is stimulated directly or merely indirectly assisted, and whether bacterial toxins are directly or indirectly inhibited or neutralized.[643] McGregor-Robertson studied the results of sulfanilamide therapy on gonorrheal partners: often one responded promptly, the other did not. It was assumed that the bacterial strains were identical. [Studies on the thermal death time of the strains were not made to certify that the partners' strains actually were identical. Sometimes they are not, as was shown by Boak, Carpenter and Warren.[3]—Ed.] If they had been identical these results would indicate that certain patients rather than certain gonococcal strains are resistant to sulfanilamide. Hence the drug acts, not directly on bacteria, but through the patients' defensive mechanism. But since the drug

does not augment the immunity mechanism specifically, Garrod advised, not the abandonment, but the supplemental use of the established methods of producing specific immunity (by serums, etc.).

Absorption, Diffusion and Excretion of Sulfanilamide. Marshall and his colleagues[621, 623, 624] reviewed previous, and reported new studies, on the absorption, diffusion and excretion of sulfanilamide and related compounds. Absorption is more rapid when sulfanilamide is given orally than when given subcutaneously. Diffusion is so readily accomplished that concentration of the drug in various body tissues and fluids is approximately equal. The relative amounts of sulfanilamide in blood, milk and cervical secretion were studied.[10] The drug appears in sweat; its concentration therein on hot days may be sufficient to reduce the urinary concentration significantly.[442] Several new and improved methods for determining concentrations of sulfanilamide in blood and other fluids were reported. Marshall and Litchfield, and Marshall and Cutting refined the original method of Marshall, Emerson and Cutting (1937) as did also Prom, Stevens and Hughes, and MacLachlan, Carey and Butler.

Toxicity of Sulfanilamide: 1. Animal Experiments. Studies on the relative toxicity of sulfanilamide in various animals were reported.[621] Free sulfanilamide is relatively nontoxic, its conjugated (acetylated) form is somewhat more toxic. Marshall, Emerson and Cutting provoked acidosis in dogs but noted no deleterious effect from sulfanilamide on the blood of dogs or rabbits, and no permanent renal damage although large doses produced transient renal insufficiency. Adair, Hesseltine and Hac noted the drug's harmful effect on the fetus of pregnant rabbits. A remarkably low toxicity of the drug for rabbits was noted by Kolmer and his colleagues: sulfanilamide provided to rabbits considerable, but not complete, protection against the development of experimental beta hemolytic streptococcic infections (including suppurative arthritis). Giving doses to rabbits comparable to those given to man, Kreutzman and Carr noted no significant effect on blood cells during treatment, but after treatment there was a 10 to 15 per cent increase in erythrocytes and in eosinophiles, moderate congestion of splenic pulp with erythrocytes, and an increase in the proportion of single-lobed eosinophiles in bone marrow: evidences of early depression of bone marrow.

2. Toxic Effects of Sulfanilamide on Humans. Another year's experience again indicates that sulfanilamide is relatively nontoxic to man. Serious reactions were rare but minor symptoms of toxicity were common. Most physicians reported that in a high percentage of their cases certain gastrointestinal and neurologic symptoms in variable amounts developed: cyanosis, lassitude, dizziness, faintness, grogginess, a "jittery feeling," tinnitus, headache, malaise, anorexia, nausea and sometimes vomiting. Often these symptoms lasted only two or three days and disappeared when the initial high doses of the drug were reduced.[643, 983] These symptoms were generally less notable among patients at rest in bed and rarely necessitated cessation of treatment but administration of the drug to ambulatory patients may have to be reduced or stopped. Because of the faintness, inability to concentrate, grogginess and disorientation developed by some ambulatory patients, such patients, particularly professional taxi or truck drivers and aviators, should be warned not to drive cars or fly.[593, 643] [Because of anoxemia sulfanilamide therapy lowers an aviator's "ceiling" by about 5000 feet. Hence passengers and air-craft employees are now prohibited from flying in England while under such therapy.[325]—Ed.] Such symptoms have already produced some automobile accidents.[24, 841] Young patients tolerate sulfanilamide better than the aged, males better than females. Children tolerate it very well.[458]

Toxic reactions have been classified[1024] as follows: (1) those which are due to a direct toxic effect of the drug and which generally vary with the dosage and the individual's tolerance (e.g., anorexia, nausea, etc.); (2)

those which are due apparently to individual idiosyncrasy (e.g., acute hemolytic anemia, agranulocytosis); these reactions bear little or no relationship to doses used; (3) those which result for unknown reasons and the significance of which is not clear: e.g., fever, skin rashes.

Sulfanilamide Fever. Of the more significant toxic reactions sulfanilamide fever was the commonest noted by Long and Bliss: it affected 6 per cent of 335 patients. Others noted it more often. Fever affected 50 per cent of the patients of Mahoney, Van Slyke and Thayer and in one rose to 105.8° F. within one hour of the (first?) dose of the drug but disappeared within 24 hours. A high fever affected 9 of Schoenrich's 60 patients, and 3 of the 115 patients of Vest, Hill, Harrill and Pitts. Fever was often accompanied by chills and rashes. Fever and chills affected 5 to 6 per cent of Ellison's patients. Generally fever of 102 to 103° F. was noted; occasionally it rose to 105 or even 106° F.[46, 388, 591, 1024] Fever was rare among children, frequent among adults.[591] Among Brown's [128] patients fever was noted, rarely before the third or fourth day, generally between the seventh and tenth days of treatment. Long noted its appearance anywhere between the first and fourteenth day of treatment. Some authors [46] recommended that when fever appears during sulfanilamide therapy administration of the drug should be stopped to see if the fever resulted therefrom; if so administration of the drug may be resumed cautiously if necessary. Others [610] stopped medication only if temperatures reached 101° F. Because early fever developed in cases in which dermatitis, acidosis, acute hemolytic anemia or agranulocytosis later developed, Long recommended that the development of even simple fever should be regarded as a warning, and administration of the drug stopped. When the fever has gone, one should give a test dose of 5 grains; if no reaction occurs within 12 hours, it is probably safe to resume treatment.

Gastrointestinal Symptoms. Mild symptoms were common and did not necessitate discontinuing doses of the drug. Occasionally vomiting, severe diarrhea, or abdominal pain, generally in upper quadrants, was noted.[591, 644] When vomiting or diarrhea affects infants, administration of the drug should be stopped.[11]

Jaundice and Hepatitis. Two types of jaundice may occur during sulfanilamide therapy: that from mild or severe hemolytic anemia, and that from toxic hepatitis. In either case use of the drug should be discontinued promptly. Two fatal cases of jaundice and hepatitis,[49] two nonfatal cases,[644] a fatal case of toxic hepatitis, jaundice and toxic erythema,[828] a fatal case of acute yellow atrophy in a patient who took more of the drug than prescribed,[191] a fatal case due either to the drug or to a coincidental biliary cirrhosis [892] were reported. Garvin noted five cases (two fatal) of toxic hepatitis reported in the literature and recorded five cases of his own (one fatal); in two of his cases and in one case previously reported exfoliative dermatitis was also a complication. Among 335 patients given sulfanilamide Long noted only one who had jaundice not arising from anemia. Rimington noted increased porphyrinuria in 8 of 12 patients on sulfanilamide. Rats so treated excreted 2 to 10 times the normal amounts of porphyrin in urine. Photosensitivity was also observed. The porphyrins isolated were coproporphyrins I and III. The latter was interpreted as indicating hepatic damage.

Cardiac Symptoms. Precordial pain was frequently noted and was generally relieved by rest in bed.[960, 989] A patient of Dozzi took 80 grains of sulfanilamide at one dose for a hemolytic streptococcal sore throat: joint pains developed the next day and four days later nodal rhythm which lasted four months.

[Were symptoms due to the drug or the infection?—Ed.]

Renal Symptoms. Long noted no renal disturbances, but others noted two cases of hemoglobinuria [591] and four cases of "chemical pyelitis." [435]

Neurologic Reactions. These included toxic psychosis, mild paranoia with audi-

tory and visual hallucinations,[459] disorientation and even mania in a few cases,[591] paresthesia,[983] dizziness and short loss of consciousness,[351] transient optic neuritis[185] hiccoughs with fever,[1053] peripheral neuritis with the clinical picture of progressive muscle dystrophy,[730] severe vertigo, dizziness, and ataxia with a positive Romberg sign in one case[388] and grogginess or disorientation of ambulatory patients sufficient to cause automobile accidents.[24, 841]

Skin Rashes. Morbilliform or maculopapular rashes frequently occurred, generally with fever.[11, 35, 185, 611] They occasionally affected infants after a single dose of the drug.[11] The incidence of such rashes among patients receiving the drug was reported variably to be 1,[593] 2,[989] 4,[591] 10,[841] 13,[610] 16,[1024] and 20[435] per cent. The rashes were often mild, occasionally severe and generally appeared between the eleventh and twenty-fourth day of treatment.[1024] In one case rash with edema of face and extremities, hemorrhagic spots and later desquamation developed.[1024] A case of "severe intractable ulcerative dermatitis" was encountered.[419] If the rashes are mild, treatment need not be stopped. If they are more marked use of the drug should be discontinued. Then the rashes usually will disappear promptly and may not reappear when the drug is given again.[185] One case deserves special mention. Rogers saw a woman who had had five minor operations performed under local anesthesia. The anesthetics were procaine hydrochloride, tutocain and butyn; all contain aminobenzene. After each of the last three operations allergic reactions appeared at the sites of injection of the anesthetic. Years later sulfanilamide (25 grains within 36 hours) was given orally for erysipelas. In the succeeding one to 10 days an acute reaction of bright red erythema, itching, swelling and tenderness appeared at the site (dermal and mucosal) of each previous injection of anesthetic. Sulfanilamide also contains aminobenzene to which the patient apparently had become sensitized. This form of allergy differed from food allergy in that the reaction occurred only in regions previously sensitized.

Articular Reaction. Nandi gave 10 grains of sulfanilamide t.i.d. to a young woman as a prophylactic measure after manual removal of placenta. Three days later her knees became painful; after three more days effusion developed, and ankles were painful. Fever and leukocytosis were present. A history of previous rheumatism was denied. Administration of the drug was stopped; the articular symptoms were reduced the next day and disappeared in three days.

[This was believed to represent a new and bona fide reaction to sulfanilamide. But is it not possible that mild articular infection occurred?—Ed.]

Acidosis. In 3 per cent of their cases, Long and Bliss noted "clinical acidosis" (hypernoia and lowered CO_2 combining power), associated with loss of sodium and potassium in urine. It could be prevented by the daily use of sodium bicarbonate in doses a third to a half that of the sulfanilamide. Strauss and Southworth noted a decrease in the CO_2 combining power of plasma, definite diuresis and an increased excretion of sodium and potassium among men given sulfanilamide. Even though large amounts of the drug were given to dogs loss of base through renal excretion was slight and always insufficient to alter the CO_2 combining power of plasma.

Cyanosis. This may result from (1) the presence of aniline black, a black oxidation product of sulfanilamide, (2) methemoglobinemia, (3) sulfhemoglobinemia. Cyanosis of variable degree affects most patients receiving the drug; its intensity usually varies with the doses used. It affects 20 per cent of children and from 50[591] to 75 per cent[1024] of adults under treatment. It is rarely due to methemoglobinemia or sulfhemoglobinemia, and cyanosis per se (without dyspnea) is not an indication to discontinue treatment.[593, 621, 1024] Fifteen cases of notable cyanosis without methemoglobinemia or sulfhemoglobinemia were reported.[90, 180] In eight such cases King and Leslie found the oxygen saturation of blood to be normal; hence oxygen therapy should not be expected to influence the cyanosis. Mull and Smith noted a case of marked cyanosis in which oxygen saturation of blood decreased from 88 to 39.8 per

cent; the oxygen capacity also dropped, but no sulfhemoglobinemia or methemoglobinemia was present. Ottenberg and Fox noted that irradiation of dilute solutions of sulfanilamide with ultraviolet light caused the development of a purple color which stained cells similarly to the hue of patients receiving the drug: perhaps a similar process causes the cyanosis in vivo.

Methemoglobinemia. This often occurs to some degree. It need not necessarily interfere with treatment. Even when marked, it disappears rapidly when administration of the drug is stopped. Oxygen therapy is helpful.[1024] Posner, Guthrie and Mattice noted four cases of cyanosis associated with an unstable methemoglobin in the blood which persisted during oxygen therapy but disappeared when sulfanilamide therapy was discontinued.

[Methylene blue given intravenously or orally will cause prompt disappearance of the methemoglobin (W. B.).—Ed.]

Sulfhemoglobinemia. This condition is more dangerous and persistent than methemoglobinemia. It may be evidenced by cyanosis and dyspnea. Administration of sulfanilamide must be discontinued. Oxygen therapy is useless. Transfusions and intravenous injections of saline and glucose solutions are indicated.[1024] [Some do not now agree with this view.—Ed.] No new cases were reported.

Leukocytosis. Kracke noted leukocytosis (25,000 to 74,000) in 6 cases. Alpert and Forbes reported a case in which leukocytes numbered 32,000 before and 39,000 after a period of granulocytopenia (leukocytes 1200) from sulfanilamide. Leukocytosis was not noted by others.[89, 90]

Leukopenia. A transient polymorphonuclear leukopenia affected 23 of 50 ambulatory patients receiving the drug.[122] In Johnston's case leukocytes in the blood decreased rapidly to 3500. Others noted no leukopenia.[89, 90, 435]

Hemolytic Anemia. A mild (10 to 20 per cent) reduction in hemoglobin, unassociated with bilirubinemia, was commonly noted.[11, 593, 610, 960] Such mild reductions do not necessitate cessation of treatment.[46, 593] Severe acute hemolytic anemia is one of the rare and serious toxic reactions. Vest, Harrill and Colston noted 18 nonfatal cases among 800 to 900 patients treated at Johns Hopkins Hospital, and 2 nonfatal cases among 300 patients at Brady Institute. Acute hemolytic anemia affected "a few" of the 250 patients of Lockwood, Coburn and Stokinger, 3 per cent of Long's 335 patients and 4 per cent of Wood's 522 patients. The condition appeared generally 24 to 72 hours after treatment was begun. Six nonfatal cases were reported.[364, 515, 697, 815, 902, 960] The lowest hemoglobin noted was "less than 25 per cent"[364]; in two cases the erythrocyte count fell to about 1,000,000 cells.[364, 515] In one case, only 30 grains of sulfanilamide had been taken.[815]

In such cases administration of the drug must be stopped at once, the intake of fluid should be large; transfusions are generally required. Bone marrow (oral), and liver extracts have been prescribed. Sometimes if patients are "alkalized" (no details) and "fluids are forced" transfusions may be unnecessary, according to Vest, Harrill and Colston.

Heretofore no fatality from acute hemolytic anemia caused by sulfanilamide has been noted. Wood reported the death of a negro from acute hemolytic anemia which developed during administration of the drug. The patient had hemolytic streptococcal infection which possibly may have been a factor in producing hemolysis, but the infection had subsided clinically during therapy. The pathologic findings were representative of any severe hemolytic anemia; no feature was considered a specific lesion from the drug.

Agranulocytosis. This represents an idiosyncrasy which has occurred generally on ordinary doses of the drug. It is often fatal: 7 of the 10 cases reported in 1937 were fatal. Fifteen new cases were reported: 10 of them were nonfatal, recovery occurring after the use of pentnucleotide, roentgen therapy over long bones, whole

blood given intramuscularly and concentrated yellow bone marrow.[22, 23, 499, 502, 591, 593, 645, 987]

Included in the 10 nonfatal cases were 2 occurring among 800 to 900 patients on sulfanilamide observed by Vest, Harrill and Colston, and one case among Long's 335 patients. Five fatal cases were reported.[77, 126, 230, 719, 847] Synopses of cases previously reported were made.[22, 499, 548, 643] In the nonfatal case of Allen and Short an absolute monocytosis began five days after circulating neutrophiles began to diminish and continued through the period of neutropenia. This was regarded as a sign of favorable prognosis since Rosenthal and Abel (1936) noticed that fewer deaths occurred from neutropenia when it was associated with an absolute increase in monocytes.

"Elixir sulfanilamide—Massengill." Further comments on this disaster appeared.[969] Another fatality from the "elixir" was noted.[629] Necropsy findings in several cases were reported.[605] Studies on the toxicity of the elixir for animals were made.[760] Deaths were due, not to sulfanilamide, but to the solvent used (diethylene glycol).

Summary. Physicians must be familiar with the protean toxic reactions to the drug and their relative seriousness, but this summary must not lead one to believe that the more serious reactions are frequent. At the Johns Hopkins Hospital no mortality occurred among 900 patients given sulfanilamide, and only one of a group of 115 ambulatory patients given the drug had to be hospitalized because of toxicity (Vest, Harrill, Hill and Pitts). West gave as much as 198 grains in one day and as much as 5000 grains over a period of weeks without noting any serious reaction. Womack cited Colston to the effect that only one death (agranulocytosis) had occurred among about 5000 cases of various diseases in Baltimore treated with sulfanilamide. But despite its being relatively nontoxic the drug is not a panacea and must be used with caution. The percentage of patients who cannot take adequate amounts of the drug because of annoying (but not necessarily serious) toxic effect was variably reported as being 5 per cent,[280] 5 to 10 per cent,[987] 8 to 10 per cent,[208] 13 per cent,[24] and 10 to 20 per cent.[46] As previously stated toxicity is usually more notable and more frequent among ambulatory patients than among those bedded at home or in hospitals. There was no relationship between the appearance of toxicity and the therapeutic effectiveness of the drug.[591]

Treatment of Toxicity. In the presence of mild toxicity (malaise, headache, nausea) full medication should be continued until the desired concentration in the blood is reached; when the quantity is reduced to a maintenance dose, these milder reactions generally disappear or become insignificant. In the presence of moderately severe toxic effect (skin rashes, diarrhea, abdominal pain) the dose of the drug should be reduced or continued with caution.[924] Some advise discontinuance of the drug for a few days to avoid more serious reactions. If mild or moderate toxic reactions do not disappear promptly when the drug is stopped temporarily, or if they promptly recur when use of the drug is resumed, sulfanilamide therapy should be abandoned in favor of other measures.[49] In the presence of severe toxic reactions (fever with tachycardia, acute hemolytic anemia, acute

leukopenia, jaundice) administration of the drug should be stopped at once, and large amounts of fluid given. Sometimes this will suffice but in most cases the special measures mentioned in connection with the individual toxic reactions are urgently required.

Prevention of Toxic Reactions. The safest way to prevent serious toxic reactions is for physicians to hospitalize patients whenever possible at least for the first week or two of treatment. Dosage can be controlled more accurately by frequent estimations of sulfanilamide in the blood. Minor toxic reactions are endured more easily. Major reactions often can be prevented or their earliest appearance detected by frequent (daily) estimations of level of blood cells and hemoglobin and close clinical observations on fever, condition of skin, etc.[11, 593] Some physicians stated that to prevent sulfhemoglobinemia patients should avoid eggs, onions, sulfur compounds, the saline and anthracene groups of aperients and laxatives (e.g., magnesium sulfate), aniline derivatives (phenacetin and acetanalid), the phenylhydrazine derivatives (antipyrine and aminopyrine) and the sulfonemethane group of drugs. If cyanosis is notable or associated with dyspnea, a spectroscopic examination of blood for methemoglobin or sulfhemoglobin should be made. [Sulfhemoglobinemia is a very rare complication: indeed some investigators doubt if true sulfhemoglobinemia ever results from the use of sulfanilamide; others doubt that it can be prevented by the measures noted.—Ed.] To prevent acidosis enough sodium bicarbonate should be given to make urine neutral or alkaline. Various doses of the alkali were recommended. Long gave a third or a half as much sodium bicarbonate daily as sulfanilamide; others prescribed equal amounts of alkali and sulfanilamide; some gave 10 grains of sodium bicarbonate with each dose of sulfanilamide; others withheld alkali until signs of intolerance appeared.[280] [One of us (W. B.) has been unable to prevent acidosis by the use of alkali and considers its use unnecessary.—Ed.] Noting a marked increase in mortality among litters of pregnant rabbits given sulfanilamide Adair, Hesseltine and Hac recommended that until more is known of the tolerance of the human fetus and of the newborn for sulfanilamide, the drug should be given only with the utmost caution during pregnancy and lactation. Mothers receiving the drug should cease breast-feeding while the drug is being excreted in their milk.

Contraindications to Sulfanilamide Therapy. No new ones were reported. In cases of marked anemia, leukopenia, renal disease or hepatic disease the drug should not be used, or, if its use is necessary, it should be given with caution.[49] Its use was not advised in acute rheumatic fever.[630, 936] Long and Bliss did not consider previous hepatic disease or jaundice to be necessarily a contraindication.

Sulfanilamide as a Prophylactic. As yet few studies have appeared on the prophylactic value of sulfanilamide in human diseases. Whitby considered it of no prophylactic value in gonorrhea. Britton regarded its use as a prophylactic in general medicine as unjustified unless there is some

reason to anticipate sepsis in an individual case. But Jones[500] recommended the prophylactic use of small doses of the drug by persons exposed to epidemics of meningococcal or hemolytic streptococcal infections, and others are reporting on its value in preventing recurrent rheumatic fever.[194, 949]

Treatment of Gonorrheal Arthritis with Sulfanilamide

Although the effects of sulfanilamide on gonorrhea in general were reported in scores of papers, only two papers specifically dealt with results in gonorrheal arthritis. Bauer and Coggeshall gave "large doses" of the drug [daily dose, ¾ grain per pound of body weight, but not over 120 grains in one day.—Ed.] to 14 patients with proved and 4 with "probable" gonorrheal arthritis. Nine (64 per cent) of the former and 2 (50 per cent) of the latter [61 per cent of the total] were "strikingly improved" 48 to 72 hours after treatment was begun. Infected synovial fluids became sterile promptly. No gonococci could be isolated from genital foci after the third day of medication. No relapses occurred. Final results were more prompt and satisfactory with this treatment than with older methods. The drug appeared to be "a specific chemotherapeutic agent." But the effective dose varied greatly: some cures were effected with 5 mg. per cent of free sulfanilamide in the blood; in other cases 10 mg. per cent or more was required. It was recommended that if definite clinical improvement is not noted 72 hours after starting "large doses," the dose should be increased. To maintain a constant level of free sulfanilamide in the blood, one-sixth of the total large daily dose was given every four hours, day and night and the intake of fluid was kept constant.

Simmons and Dunn treated 5 cases of gonorrheal arthritis with rest in bed and sulfanilamide (80 grains daily for two days, 60 grains for two days, 40 grains for seven days). Three patients were free of pain in two days and returned to work within 12 days. One patient was relieved promptly of all symptoms within 72 hours, but he then fell and injured the affected knee. The resulting effusion was not affected by sulfanilamide, rest and heat. Prolonged treatment for one year was required for complete recovery. One patient noted prompt and complete relief of arthritis, but apparently the genital focus was not cured. A month later an articular and pelvic exacerbation occurred which failed to respond to rest, local treatment and sulfanilamide, doses of which had to be small because of poor tolerance. She then was given 40 grains of sulfanilamide daily for three days followed by fever treatment (10 hours at 106° F.). Genital and articular symptoms promptly disappeared.

To obtain a broader view of the situation than that presented by these two short reports we reviewed about 50 papers on sulfanilamide therapy of gonorrhea and found the following scattered remarks about results in gonorrheal arthritis. Among 633 cases of gonorrhea treated by Cokkinis and McElligott were nine of gonorrheal arthritis in all of which cure occurred

within three weeks, two cases of "gonorrheal synovitis" which "yielded rapidly" to the drug, and eight of fibrositis six of which were cured within four weeks. These workers developed a special plan of sulfanilamide therapy which will be discussed later. Among Sorenson's 25 cases of gonorrhea were four of gonorrheal arthritis. The patients were given sulfanilamide: 80 grains for one day, 60 grains for one day, 30 grains for 10 to 25 days; three of the four patients were cured within four weeks. [No details of these cases were given. Results were not obtained very promptly.—Ed.] Stevens gave the drug (dose unstated) to four patients with gonorrheal arthritis: its use was discontinued in one case because of a toxic reaction. "Two cases did very well and the fourth case was benefited but not as quickly." Cook and Buchtel treated "a few cases" of gonorrheal arthritis: results were "variable." Daily dosage of sulfanilamide was 75 grains for two to three days, 60 grains for two to three days, then 40 grains for the remainder of the 14 days' course.

Six of the 158 patients with gonorrhea seen by Alyea, Daniel and Harris had gonorrheal arthritis. Sulfanilamide was generally given thus: 90 grains for one day, 45 grains daily for the next 13 days. The joints became "well" in one case, "much improved" in four cases and were unimproved in one case. Genital foci were cured in only two of these six cases. Admittedly estimations of sulfanilamide in the blood had not been done satisfactorily, hence no final conclusions as to the value of the drug in arthritis could be made. "Striking results" in two cases of gonorrheal arthritis were noted by Brunet, Reinhardt and Shaw, although small doses (not over 40 grains daily) were given. Such doses proved unsatisfactory to these physicians in the management of nonarticular gonorrhea.

Satisfactory and generally prompt (within 5 to 10 days) cures in single cases of gonorrheal arthritis were reported without detail by Adler, McGregor-Robertson, Nair, and Townsend and Mulcahy. Moderately large doses were used. King mentioned an unstated number of patients with gonorrheal arthritis "miraculously cured"; dosage was 80 grains for one day, 60 grains for one day, 30 to 40 grains daily "thereafter." Results in an unstated number of cases of gonorrheal arthritis treated by Clark and Branham were "disappointing"; the daily dosage was 60 grains for two days, 40 grains for five days, 30 grains for seven days.

[Little or no details were given concerning these cases. It will be seen that, although the full doses originally recommended by Long (1937) and by Colston, Dees and Harrill (1937) were occasionally used, most cases were treated by smaller doses which we believe are likely to be inadequate at least in some cases. Nevertheless when results in all these cases are summarized (in so far as they can be) it appears that in 38 (70 per cent) of 54 stated cases the gonorrheal arthritis was rather promptly cured; in 16 cases (30 per cent) it was either unimproved or improved but not cured by sulfanilamide.—Ed.]

Gonorrheal rheumatism developed in two cases of genital gonorrhea during treatment with sulfanilamide: in one instance "tenomyositis" occurred,

but the patient was receiving rather small doses (60 grains daily for two days, 50 grains for six days, 45 grains for six days).[887] Despite fair sized doses (80 grains daily for two days, 60 grains for two days, 40 grains daily for eight days more) another patient on the eighth day of treatment developed arthritis, conjunctivitis, iritis and herpes zoster, and did not recover for five or six months.

[The exact value of sulfanilamide in the control of gonorrheal arthritis will not be known until many more cases have been carefully studied as to the presence or absence of intra-articular gonococci, and then properly treated with full doses of the drug. It is our opinion that the highest percentage of cures is obtained with levels of 10 to 15 mg. free sulfanilamide in 100 c.c. of blood.—Ed.]

Sulfanilamide for Nonarticular (Urogenital) Gonorrhea

The early reports (1937) on the effect of sulfanilamide on gonorrheal urethritis were almost unanimously enthusiastic. Eight of these early reports were tabulated by Vest, Harrill and Colston as follows:

Author (1937)	Acute Gonorrheal Urethritis, Cases Treated	Satisfactory Results Obtained	
		Cases	%
Reuter	100	92	92
Herrold	30	15	50
Buchtel and Cook	21	19	90
Orr	104	92	88
Crean	100	90	90
Cokkinis	250	200 (estimation)	"80+"
Erskine	29	21	73
Watts, Oden and Gordon	72	58	80
Total	706	587	83

In summary, "satisfactory results" were obtained in 83 per cent of 706 cases. In contrast to the good results noted by the majority were the poor results of Herrold (1937), which Vest, Harrill and Colston attributed to inadequate dosage of sulfanilamide, and the "unsatisfactory" results reported by Anwyl-Davies (1937).

To see whether these early optimistic opinions were supported by the experiences of another year we reviewed about 50 later reports (1938) on the effects of sulfanilamide on urogenital gonorrhea. We have attempted to make a statistical summary of 46 of these recent reports (table 1). It is difficult to know how accurate such a summary can be or how much significance can be attached to it. There were many variables. Among the cases treated were all types of acute and chronic urogenital gonorrhea with and without complications. There was great diversity in the method of dosage and management of the cases. Standards of "cure" varied considerably. In some cases a "cure" was apparently based mainly if not solely on disappearance of symptoms, in other cases on relief of symptoms plus the appearance of (a variable number of) "negative" smears (not cultures). Some authors observed more rigid standards of "cure" and maintained a more satisfactory and longer follow-up period of observation before reporting a cure. (If this is not done patients and physicians will learn to their sorrow that "the most sensitive media or test of cure are the urethra of the husband and the eye of the child" [Rorke]). Despite these variables table 1 is given for what it may be worth and will at least give some idea of the present status of this form of therapy.

TABLE I

Results from Sulfanilamide in Nonarticular Gonorrhea (1938)

Reporter	Cases Treated	Cures Reported		Dosages Used L = large M = moderate S = small
		Cases*	Per cent	
Adler	36	28	78	L
Ainsworth	250	193	77	L
Alyea, Daniel and Harris	158	—	75 acute 50 chronic	M
Bauer and Coggeshall	18	17	94	L
Benson	22†	4	18	—
Berry	50	Results disappointing		S
Brunet, Reinhardt, and Shaw	—	Expect 10 % cures		S
Burns	—	Results not good		S
Butler, W. W. S.	124	—	"About 75"	M
Chisholm	187	75	40	L
Clark and Branham	—	—	85	M
Cokkinis and McElligott	633	—	80–90	M
Ellison	100	68	68	L
Evans, K. L.	214	146	68	M
Goodwin	25	19	76	S
Grodberg and Carey	32	27	84	S
Harris	—	—	33	S
Hering	46	34	74	M
Herrold	50	17	34	M
Hoberg and Reck	50	28	56	M
Hoffman, Schneider, Blatt, and Herrold	25†	11	44	M
Holmes, Jones, and Gildersleeve	42†	8	19	M
Horowitz	12	7	58	M
King	87	—	"Under 10"	M
Mahoney, Van Slyke, and Thayer	205	174	85	L
Manor	33	28	85	M and S
McCuskey and McCuskey	80	56	70	M
McGregor-Robertson	100	75	75	L
Mitchell, D. R.	137	42	31	L
Nair	27	25	93	M
O'Hanlon	101	82	81	M
Randall, Krusen, and Bannick	16	15	94	M
Rock	40	32	80	S
Schoenrich	60	—	"Striking"	L
Shih and Hsiung	41	4	10	S
Sichel	35	25	71	S
Sinkoe	85	72	85	M
Snowden and Bell	15	8	53	S
Sorenson	25	22	88	M
Spink and Gaston	21	18	86	M
Spooner	33	15	45	M
Townsend and Mulcahy	90	81	90	L
Van Slyke, Thayer, and Mahoney	100	84	84	L
Vest, Harrill, and Colston	125	—	80+	M
Vest, Harrill, Hill, and Pitts	115	Expect 60% cures		L
Womack	—	—	40–50	M
Total	(3645)			
Total in which results were enumerated	2293	1540	67	

* Number stated or estimated from percentage stated.
† Juvenile vaginitis.

Results were quite variable, "cures" being obtained in from 10 to 94 per cent, which is, to say the least, quite a spread! Because of incomplete data the total results of all the reports in table 1 cannot be estimated, but, summarizing the addable figures, there were 2293 cases of gonorrhea in 1540 or 67 per cent of which the patients were presumably cured. This figure is definitely, although not strikingly lower than that obtained by analyzing the small group of 1937 reports (83 per cent of patients cured). In part it probably represents a more critical appraisal of results, a swing away from overenthusiasm. But the two groups were not entirely comparable. During the early work (1937) with sulfanilamide most patients were hospitalized for close supervision of therapy by research investigators able to gauge the necessary dosage by estimation of blood sulfanilamide. The more recent figures concern large numbers of ambulatory patients not subject to as careful supervision. Since ambulatory patients generally cannot tolerate (or were not given) as much sulfanilamide as hospitalized patients, a distinct difference in dosage was apparent. Indicated in table 1 is our estimate of the dosage given by the various workers. Because of the great differences in the dosage schemes used, classification was often difficult. In general "large dosage" indicates the approximate use of those fairly high doses originally advocated by Long and Bliss (1937) and by Colston, Dees and Harrill (1937): full initial doses (generally 80, rarely 120 grains, daily) for the first few days; then a gradual reduction. "Moderate dosage" indicates the use of initial doses generally around 60 grains for three or four days and then a reduction, but also some instances are included in which 80 grains were given for only one day and then the dose was rapidly reduced to 30 or 40 grains. "Small dosage" indicates the use generally of initial and subsequent doses not more than 40 or 50 grains, sometimes never more than 20 grains, daily.

A survey of the individual reports tended to strengthen impressions based on our own experiences that best results are undoubtedly obtained when full dosage is applied. However, an analysis of table 1, rearranged according to dosage, does not of itself lend much proof for this belief. Of a total of 1223 patients presumably treated by large doses 837 or 68.4 per cent were cured. Of a total of 860 patients given "moderate doses" 584 or 67.9 per cent were cured, suggesting that there is no special merit in the use of full doses as results with moderate doses were almost identical. [But in these cases of gonorrhea the difference between "large" and "moderate" doses was not great. The large doses used in these cases were *not* the high doses used in more serious diseases.—Ed.] Of 188 patients given small doses 115 or 61.1 per cent were cured, a difference which is definite but not as striking as one might expect. These figures merely confirm observations noted in the discussion on treatment, to the effect that although full doses are generally more effective than small doses, other factors than dosage influence the end results.

Poor Results, Failures and Comments Thereon. Poorest results were noted in cases of juvenile gonorrheal vaginitis: results in three series were satisfactory in only 18, 19 and 43 per cent of cases.[76, 458, 465] A number of writers were pessimistic about their results. Thus Brunet, Reinhardt and Shaw do not expect cures in more than 10 per cent of cases of anterior urethritis (small doses of the drug, not over 40 grains a day, were used). Some[10] called the routine use of sulfanilamide for gonorrhea "unwarranted." Delighted with his preliminary successes in obtaining rapid symptomatic cures in "almost 100 per cent of cases," King noted such a dis-

couraging frequency of bacteriologic remissions that he condemned the sole use of sulfanilamide for gonorrhea as "extremely hazardous," productive of real or bacteriologic cures in only about 10 per cent of his cases (doses used: 80 grains for one day, 60 grains for one day, 30 to 40 grains daily thereafter). Shih and Hsiung obtained symptomatic cures in 56 per cent but bacteriologic cures in only 10 per cent of their cases. Likewise, Mitchell noted satisfactory relief of symptoms in 75 per cent, but bacteriologic cures in only 31 per cent of his 137 cases. Other reports were also rather pessimistic.[80, 143, 185, 419, 438, 899, 1043] These and other writers stressed the great danger that sulfanilamide therapy will foster many "false cures," and raise a great crop of gonococcal carriers in persons whose symptoms cleared so satisfactorily and promptly that they or their physicians discontinued medication before a true bacteriologic cure resulted. To avoid this danger physicians again stressed the importance of continuing to give sulfanilamide for several (generally 7 to 16) days after all symptoms have disappeared, and thereafter rigidly and repeatedly examining the patients by cultures (rather than smears) for gonococci and by provocative tests, and so forth, to uncover any symptomless bacteriologic recurrence which, if present, should be promptly treated by another course of sulfanilamide or otherwise. Jones [504] stated that the use of sulfanilamide had not [yet.—Ed.] lowered the general incidence of gonorrhea in the state of Washington; he warned that, because the drug changes the characteristics of gonococci seen in stained smears, physicians must now exercise greater care in taking, staining, and studying smears than ever before.

Reasons for failure can be summarized as follows: 1. Inability of some patients (10 to 20 per cent) to take adequate amounts of the drug.[46] 2. Insufficient dosage given to patients who could take full doses. Ambulatory patients are often given too small doses; if their dosage is ineffective they should be hospitalized for seven to ten days of full medication.[989] 3. Premature cessation of treatment; medication stopped two to seven days after symptomatic cure and not continued until bacteriologic cure is obtained. 4. Inadequate follow-up examination to detect uncured symptomless infection. Recurrences are likely because sulfanilamide does not raise a patient's immunity to gonococci, and too many gonococci in deep seated foci, e.g., submucosal glands, do not come in contact with the drug.[542] 5. Resistance of certain patients (or strains of gonococci) to sulfanilamide; even adequate or full dosage does not result in cure. Smears and cultures occasionally remain positive even when the concentration of free sulfanilamide in blood is 9.6 to 25 mg. per cent (Adler). Concentrations in the blood were about the same in 16 failures as in 16 successes.[988, 989] 6. Excretion of two forms of the drug in urine in abnormal proportions. Usually 80 per cent of the drug is excreted as free sulfanilamide and about 20 per cent as the conjugated (or inactive) form. Occasionally equal amounts of both forms are present. Some physicians [24, 438] conjectured that perhaps there is present in the blood and tissues of patients unresponsive to sulfanilamide an abnormally

large percentage of the inactive (conjugated) form. However, in one group not benefited by the drug normal proportions of the two forms of the drug were found in the blood.[24]

Additional reasons for failure were suggested by Cokkinis and McElligott: 7. In a high proportion of their cases classed as failures the patients had enlarged prostates. 8. A small proportion of failures were due to other local complications (e.g., urethral stricture; calculous prostatitis, Tyson's adenitis). 9. The most important cause of failure was believed to be improper timing in the use of the drug. Cokkinis and McElligott insist that a degree of immunity is essential for optimal results with the drug. Of factors influencing their results, the duration of the disease preceding treatment proved to be "by far the most important." Whereas "good results" were obtained in from 72 to 78 per cent of cases in which treatment was begun during the first seven days of the disease, similar results were obtained in 92 to 98 per cent of those cases in which medication was not begun until from eight days to six months after their disease began. Furthermore the frequency of relapses and complications decreased with increasing chronicity of the disease when treatment was begun. The marked improvement in results noted in cases not treated until early in the second week of the disease "could have only one explanation—that it takes that much time for the body to acquire enough immunity to dispose of the organisms arrested by sulfanilamide." Hence according to these writers it is inadvisable to use sulfanilamide too early in the course of the disease. The correct time to start treatment with sulfanilamide is the eighth to tenth day of the disease. Treatment during the first week reduces the chance of success from a single full course by 50 per cent and the chance of ultimate success (after an additional course) by 25 per cent. A somewhat similar view was expressed by Harrison, and others[24] agreed that a week's delay in treatment was not disadvantageous.

[This is an interesting concept; other investigators should restudy their results in the light of this. The statistics of Cokkinis and McElligott seem to have been carefully analyzed and the data as given by them make a forceful argument. But the studies of one of us, W. B., have failed to support this concept. Until it is proved, delay in instituting treatment seems unfair to the patient and productive of a greater incidence of complications.—Ed.]

Good Results: Summary and Comment. In contrast to the rather disappointing results just reported were the very good results noted by the majority, "cures" being frequently obtained in 75 to 85, occasionally even in 90 per cent, of cases treated. Writers spoke of the drug as of "inestimable value"[208] and of its results as "very striking," "dramatic," "very prompt and satisfactory," "remarkable," "almost miraculous." Best results were generally noted in uncomplicated urethritis. Differences of opinion existed as to whether acute or chronic gonorrhea was more readily controlled by sulfanilamide. According to one report[24] acute prostatitis responded much more readily (75 per cent of patients cured) than chronic

prostatitis (50 per cent cured). Chisholm's results in acute and chronic urethritis were equally good. According to Hering chronic gonorrhea of males responded better (88 per cent cured) than acute gonorrhea (66 per cent cured). Mitchell noted more "symptomatic cures" but fewer real or "bacterial cures" in acute than in chronic cases.

Three control studies were of interest. Steele-Perkins stated that 50 patients treated by older methods required an average of 89 days, whereas 50 patients given sulfanilamide required an average of only 32 days to obtain satisfactory results, and there were fewer complications in the latter group. Scarcello's 105 patients were divided into three groups: those given "irrigation treatments" took about twice as long and those receiving Corbus-Ferry vaccine took almost three times as long to be cured as those given sulfanilamide. McGregor-Robertson treated 100 patients with acute uncomplicated gonorrheal urethritis with irrigations (65 per cent were cured) and 100 with sulfanilamide alone (60 per cent were promptly cured). Results in the latter group were obtained 5 to 7 times faster and the number of complications was greatly reduced. On the basis of their experience in the treatment of over 1000 cases of gonorrhea with sulfanilamide and related compounds Cokkinis and McElligott regarded sulfanilamide as "much the most efficient," its only drawback being its toxicity.

Most workers, even those disappointed in the results of the drug on local genital lesions, agreed that sulfanilamide therapy had sharply reduced gonorrheal complications (arthritis, etc.).[610, 632, 638, 887] The reduction was estimated to be more than 85 per cent by some (Cokkinis and McElligott), about 75 per cent by Alyea, Daniel and Harris, who noted practically no complications except among patients who had not received sulfanilamide. Previously about 42 per cent of gonorrheal patients had complications of one sort or another (Goldstein, cited by Alyea, Daniel and Harris). Alyea and his colleagues compiled the recent statistics of five workers who had treated with sulfanilamide 830 cases of gonorrhea, *in none of which complications developed.*

[It seems probable that regardless of whether the general incidence of genital gonorrhea is notably reduced or not, the incidence of gonorrheal arthritis will be markedly lowered as more and more patients begin early sulfanilamide therapy. Some physicians go so far as to prophesy that gonorrheal arthritis (which is regarded as affecting only about 3 per cent of patients with gonorrhea anyhow) may disappear. It is too early to make such a prediction, but some significance may be attached to the fact that, omitting the two reports which specifically and solely dealt with 23 cases of gonorrheal arthritis, we found mention of only an additional 31 cases of gonorrheal arthritis in a series of papers which concerned about 2247 cases of gonorrhea: instead of an incidence of 31 cases the expected incidence (at a rate of 3 per 100 cases) should have been 67 cases.—Ed.]

Method of Administration of Sulfanilamide: General Comments. In the matter of sulfanilamide therapy American physicians again exercised their rights to be individualistic; few of them followed the dosage-scheme proposed by the early workers in the field; they tried all manner of variations. But they [128, 840] generally subscribed to the following principles: in serious, potentially lethal diseases (e.g. puerperal sepsis,

meningococcal and serious hemolytic streptococcal infections) full doses were generally used, large initial doses, 120 to 180 grains daily until the desired concentration in blood was attained, and then reduction of dose. In such cases one group of physicians [610] gave one large initial single dose (100 grains or more), followed by high but smaller doses for 12 days only, and noted no serious toxicity. According to McGinty the largest published dose was that of Foulis and Barr (1937) given for puerperal sepsis: daily 215 grains for four days, 110 grains for three days; a total of 1190 grains (79.2 gm.) in seven days. [Bauer and Coggeshall gave a total of 1440 grains in 24 days to a patient with atrophic arthritis; the only toxic manifestation was cyanosis.—Ed.] For moderately severe diseases (e.g., gonorrhea) moderately high (80 to 120 grains daily) doses were first used, then a reduction when concentration in blood was adequate. For mild illnesses (e.g., urinary tract infections) small initial doses (30 to 40 grains daily for two or three days) were used and then the dose was *increased*. All the doses noted herein apply to adults unless otherwise stated. Jones [500] regarded the following plan as the accepted standard:

Oral Doses for 24 Hours, Grains

	Mild Infection	Severe Infection
Infants up to 40 pounds	15–25	30–50
Children 40–80 pounds	35–45	70–90
Older children 80–120 pounds	50–60	100–120
Adults	60–80	120–160

To obtain optimal results it is important to regard these points: 1. As early as possible one should produce as high a concentration of free sulfanilamide in blood as seems desirable for the disease under treatment and within the limits of a patient's tolerance. The early high dose should be continued until symptoms definitely improve (generally within three or four days) and the smaller maintenance doses should be continued (at least one or two weeks more) until a bacteriologic, not just a clinical, cure is obtained. *The continuing doses are of the greatest importance to prevent relapses and recurrences.* 2. Since maximal therapeutic effects often occur as early as the third or fourth day of medication the high initial doses are generally reduced about the fourth day. 3. To keep the concentration in blood about constant, doses should be given at evenly spaced intervals as far as possible both day and night. 4. For the same purpose the daily intake of fluid should be constant. (Differing daily amounts were allowed: 1200 to 1400 c.c.,[128] 1500 c.c.,[610] 2000 c.c.) [24]

Scheme of Dosage for Gonorrhea and Gonorrheal Arthritis. For the following reasons most physicians did not favor the use in gonorrhea of the large doses previously noted: 1. Gonorrhea is rarely lethal. 2. Most patients being treated are ambulatory. Although hospitalized patients can often tolerate 80 grains or more daily, ambulatory patients can rarely tolerate over 60 grains daily.[439, 649] 3. Experience shows that many gonorrheal patients are relieved of symptoms by rather moderate doses (40 to 50 grains daily).[439] Bannick, Brown and Foster noted that gonorrheal patients seemed to get good results with concentrations in blood of 5 to 7 mg. per cent and that concentrations of 10 mg. per cent were not required. Manor's results were the same in one group given moderately high doses (daily 70 grains for two days, 60 grains for three days, 20 grains for eight days) as in another group given low doses (22½ grains daily for 7 to 17 days). 4. The use of only

moderately high doses reduces the incidence of certain (but not all) complications and toxic reactions.

As an extra precaution to prevent toxic effects and control dosage some physicians gave no prescriptions for the drug, but dispensed from their offices the proper amount of pills for each dosage period, generally just enough for two to three days.[185, 280] Others gave prescriptions for just enough for each period of similar dosage, and stressed the importance of marking all prescriptions "No refill."[873]

Schemes of dosage for gonorrhea followed these general patterns: 1. Dosage was based on mathematical calculations to maintain concentrations in blood of 5 to 10 mg. per cent free sulfanilamide. Some workers based their dosage on a general plan of about 15 grains to every 20 pounds of body weight as the probable requirement to maintain the desired concentration.[11, 500] Calculating a tentative dose from the patient's weight but keeping their eyes on the concentration in the blood, they increased or reduced the dose as necessary to maintain the decreed concentration regardless of the patient's weight. To attain quickly and maintain the concentration desirable in gonorrhea Long recommended the following dose for (150 pound) adults: an initial single dose of 80 grains, then 20 grains every four hours for four or five days, then smaller doses given 10 days more to males, 25 days more to females. If there is no notable clinical response after the first four or five days, further sulfanilamide therapy probably will fail; other therapy should be used. Some[185, 280] criticized the use of these full doses as intolerable for most gonorrheal patients and likely to court complications.

[We cannot agree.—Ed.]

2. A "routine" dosage used which is not based on the patient's weight, consisted of a rather high early daily dosage (generally 80, rarely 120 grains), then a reduction. Having first used smaller doses in gonorrhea, Colston, Dees and Harrill (1937) later felt obliged to increase their daily dosage to 80 grains for two days, 60 grains for five days, 40 grains for seven days, 20 grains for 14 days. Mahoney, Van Slyke and Thayer[610, 983] considered the short use of large doses less toxic and more desirable than the longer use of small doses. They recommended for patients over 135 pounds, 120 grains daily for four to six days, then smaller doses for a total of only 12 days; for others they started with 80 grains daily for five to nine days. McGregor-Robertson also approved of the short use of large doses: 120 grains daily for three days, 96 grains for seven to eleven days. Others used full but slightly lower doses: Ellison, 80 grains daily for four days, 60 grains for three days, 40 grains for fourteen days, 20 grains for seven days; Cook and Buchtel, 75 grains daily for two to three days, 60 grains for two to three days, 40 grains for a total of fourteen days; then a rest period of ten to fourteen days, then *always* a second course to prevent recurrences; Vest, Harrill, Hill and Pitts, single first dose of 70 to 110 grains, then 60 to 100 grains daily; Alyea, Daniel and Harris, 90 grains for one day, 45 grains for thirteen days.

[To determine for himself how important the factor of dosage is the reader can note in table 1 the results obtained when these doses were used.—Ed.]

3. A routine scheme used (not based on patient's weight) consisted of moderate initial doses, then reduced doses. This scheme was followed by several.[46, 49, 185, 438] The highest doses given were generally 60, rarely 80 grains; thus Ballenger and his colleagues gave 60 to 80 grains daily for two or three days, 40 to 50 grains for five days, then smaller doses.

4. Another routine scheme consisted of a low or moderately low dosage which is unchanged. Unwilling to use larger doses because of toxicity Burns gave only 20 grains daily. Grodberg and Carey gave only 20 to 30 grains daily to women for four

to six weeks. 5. Early low or moderately low doses, later reduced even more, were given [80, 130, 862]; for example Butler gave 45 grains daily for four days, 25 for seven to ten days. 6. Early low doses were later increased.[810] Because of a "genuine respect" for the toxic properties of the drug, Harris first gave a "test dose" of 15 to 20 grains daily "for a certain period," thereafter no higher than 40 grains daily. 7. Combined oral and intramuscular administration of sulfanilamide has been suggested to maintain more readily its even concentration in the blood and it was used by Ainsworth. It satisfied the type of patient who likes "shots," the red color in urine had a good psychic effect, the need for injections brought patients regularly to the office and led to more careful and successful supervision. 8. Sulfanilamide therapy continued with other measures will be discussed later.

Duration of Medication. This also varied considerably, and the drug was given: only four days,[374] two to six days only,[983] four to six days only [960]; high doses, however, were given. It was given by others for eight days,[688] "not over ten days," [841] ten to fourteen days,[644] twelve to fourteen days,[185, 208, 435, 887] "at least fourteen days," [11] for twenty-one days,[199, 458, 865] "at least twenty-one days," [183] not over twenty-one days regardless of the status of the disease,[438] twenty-eight days (moderate doses),[453, 1043] for four to six weeks (small doses).[393]

Conclusions as to the Present Status of Sulfanilamide Therapy for Gonorrhea and Gonorrheal Arthritis

The *advantages* of sulfanilamide therapy for gonorrhea and its complications are many. The drug is easy and cheap to administer. It is essentially nontoxic, rarely producing serious reactions. It promptly cures genital gonorrhea and gonorrheal arthritis in about 70 per cent of cases even though it must often be given to ambulatory patients for whom dosage cannot be controlled satisfactorily. Its prompt use notably lessens the incidence of complications or generally controls rapidly those already present.

Its *disadvantages* are becoming more obvious. It occasionally provokes serious, even fatal toxic reactions; it very commonly produces reactions which, though mild, are quite annoying. Effective doses of it cannot be taken by 10 to 20 per cent of patients. By the methods so far used it has failed to cure about 30 per cent of patients with gonorrhea and an equal number of those with gonorrheal arthritis. Because it is so often effective clinically more rapidly than bacteriologically, it may lead to "false cures" when medication is stopped prematurely as is a constant danger. Its rational use demands careful prolonged bacteriologic diagnosis and control.

The attitude of urologists was summarized by Mathe and Spitalny from answers (number unstated) to questionnaires sent to 150 American and European urologists. On the basis of these replies it was judged that 90 per cent of the profession were using the drug; its distinct advantages (as noted previously) were fully recognized but it was considered quite toxic and its optimal dose difficult to establish (only one urologist advocated initial daily dose of 120 grains; the average daily doses used were 80 grains for two days, 50 grains for one day, 15 grains thereafter). Results therewith had not been as spectacular as originally reported, hence 85 per cent of the urologists replying regarded sulfanilamide merely as the most valuable *adjunct method* ever devised for gonorrhea, but one which should be more

or less routinely supplemented by additional therapy: generally local chemotherapy, occasionally supplemental fever therapy or vaccine therapy.

No final appraisal can be made without considerable further experience. Obviously much standardization is needed: standardization of the method of administration, the timing, dosage and duration of medication, and especially standardization as to the criteria of "cure." [292] At present the best criterion of cure is repeatedly negative *cultures* at suitable intervals; according to Long that should be the sole criterion. Some physicians already consider sulfanilamide for gonorrhea outdated by the use of sulfapyridine or other compounds. This remains to be proved; meanwhile these data on sulfanilamide will serve as a yardstick with which to measure the successes of other compounds.

Combined Therapy of Gonorrhea: Sulfanilamide Plus Other Measures

1. Sulfanilamide Plus Local Chemotherapy. Several physicians [374, 439, 841, 865, 873, 899] noted enough failures from the use of sulfanilamide alone for them to combine such therapy with orthodox local genito-urinary chemotherapy; many patients not cured by the first method were cured by the combination. To Sinkoe the main advantage of such combined therapy was that it compelled patients to return to his office frequently enough for close supervision and minimized the chief danger of unsupervised self-treatment, i.e., the cessation of treatment when symptoms improve before bacteriologic cure occurs. It is not surprising that Burns who only gave 20 grains of sulfanilamide daily, found it necessary to use local chemotherapy also. Ainsworth used combined oral and local therapy to obtain cures in 16 per cent of one series of 148 cases [14] and in 36 per cent of 230 other cases [15] in which sulfanilamide alone was ineffective. Others [888] recommended employment of additional local therapy "as if sulfanilamide were not being employed." According to Ballenger and his colleagues nearly all cases of early gonorrheal urethritis can be promptly cured by combining proper doses of sulfanilamide (early doses 60 to 80 grains) with the sealing (by collodion) of a 5 per cent solution of mild silver protein (argyrol) in the anterior urethra on four successive days: "This is surprising because a comparatively high percentage of failures occur when either procedure is used alone." They treated 79 consecutive patients by this method with only two failures.

[It is important to determine whether the combined method is actually superior because of the additional use of local treatment or simply because the sulfanilamide therapy was better controlled as a result of frequent office visits.—Ed.]

2. Sulfanilamide Plus Vaccines. For reasons noted previously Cokkinis and McElligott delayed the use of sulfanilamide until after the eighth day of the infection, but "vaccine" injections were begun at the onset of infection and continued through the three weeks of sulfanilamide therapy in order to stimulate "enough immunity to dispose of the organisms arrested

by sulfanilamide." If necessary a second course was given by this method. "Total permanent cures in male patients can be increased to over 90 per cent."

3. Sulfanilamide, Vaccine and Local Chemotherapy. This combination was used by King in a few cases, also by Mathe who considered that the supplemental use of Corbus vaccine gave better results than when one remedy alone was used.

4. Sulfanilamide with or Followed by Fever Therapy. Several physicians stressed the curative value of sulfanilamide combined with or followed by fever therapy in the treatment of cases resistant to either method alone. Randall, Krusen and Bannick treated two groups of women with gonorrhea: cures were obtained in 29 (94 per cent) of 31 patients treated by fever therapy alone (one 10 hour session) and in 15 (94 per cent) of 16 patients given sulfanilamide alone. Thus each treatment failed to cure an equal percentage of cases. One patient resistant to sulfanilamide was promptly cured by fever and one resistant to fever was cured by the drug. Cures in gonorrhea can therefore be expected in almost all cases if one or both methods are used. Cook and Buchtel noted four gonorrheal cases resistant to sulfanilamide: three patients were cured by subsequent fever, and one with particularly resistant gonorrhea was cured by a combination of sulfanilamide plus fever (10 hours of general fever including 5 hours of supplementary pelvic heating). They recommended that cases of gonorrheal arthritis not notably relieved by three to six days of sulfanilamide should be promptly subjected to fever therapy. Elkins and Krusen cured by sulfanilamide two patients with gonorrheal arthritis resistant to the usually adequate amounts of fever, and cured by fever therapy nine of ten resistant to the drug alone. They prescribed 80 grains of the drug daily for two days prior to fever therapy (generally one 10 hour session at 106° F.). Eight cases of gonorrheal arthritis were successfully treated by Rock with fever plus sulfanilamide. One of Simmons and Dunn's patients with gonorrheal arthritis resistant to the drug alone was cured by the combined method: 40 grains of the drug daily for three days, then 10 hours of fever at 106° F. Atsatt prescribed 60 grains of the drug the day before a fever session (7 hours at 104 to 105° F.). Without giving details he stated that results from two or three such periods were more successful than from either alone, insuring "an almost perfect result." "Fascinating results" were noted by Ballenger, Elder, McDonald and Coleman who obtained by the combined methods "spectacular cures of stubborn cases" of gonorrhea unrelieved by either remedy alone. The drug (60 to 80 grains daily) was given for one to two days before the first fever session, and was continued between sessions of fever. Three fever sessions were generally given, one every other day. Of 31 patients with gonorrhea treated thus, 24 were cured within a week; 4 of them had gonorrheal arthritis. Some physicians suggested that when the combined method was used, smaller amounts of both fever and drug were effective. According to Wengatz, Boak and Carpenter

the thermal death time of gonococci at 41.5° C. was shortened by about 50 per cent when enough sulfanilamide was added so that blood broth cultures thereof contained a concentration of 10 mg. per cent. The fever sessions of Ballenger and his colleagues were only three hours at 104° F. Heald considered a fever of 102 to 104° F. by inductothermy adequate (detailed results and hours of fever unstated). However, Kendell (cited by Elkins and Krusen) and Elkins and Krusen found it necessary to use full, not abbreviated, fever sessions even when the drug was also used. To 11 patients with gonorrhea uncured by sulfanilamide, in "several" of whom arthritis had developed during medication (doses variable, some small, some moderately high), Owens, Wright and Lewis gave a conditioning fever treatment (three hours at 103 to 104° F.) and on the next day a full session (10 hours at 106 to 107° F.). Ten of the eleven patients were promptly cured clinically and bacteriologically. The other patient remained uncured but finally responded to subsequent sulfanilamide therapy (though previously resistant to it) as if the fever had made him more amenable to the drug.

Horowitz, however, deprecated the combined method because of the disturbing cyanosis he observed in three cases so treated: "If we add to the anoxia of fever therapy the additional danger of anoxia caused by sulfanilamide we are exposing our patients to a double hazard."

[This opinion, based on such a small experience, is contradicted by the larger experience of others.—Ed.]

Treatment of Gonorrhea by Newer Sulfonamide Compounds

Terminology 1. Dimethylated disulfanilamide = sulfanilyl dimethyl sulfanilamide. Synonyms: Diseptal A; uleron; uliron; dimethyl-disulfanilamide.

Terminology 2. Monomethylated disulfanilamide = sulfanilyl monomethyl sulfanilamide. Synonym: Diseptal B.

Terminology 3. Nonmethylated disulfanilamide = sulfanilyl sulfanilamide. Synonyms: Diseptal C; disulon; disulfanilamide. The term "disulfanilamide" is restricted by some to mean the third compound (i.e., disulon or diseptal C); by others it is used to include any of the aforementioned disulfanilamide compounds; hence to them [1031] disulon, uliron and "sulfanilyl sulfanilamide" are all disulfanilamide.

Terminology 4. Soluseptasine = disodium para (gamma phenyl-propylamino) benzene sulfonamido-alpha-gamma-disulfonate.

Terminology 5. Sulfapyridine = 2-sulfanilamido pyridine or 2-p-aminobenzene-sulfonamido pyridine. Synonyms: M. and B. 693; dagenan.

1. Uleron, Uliron, Dimethylated Disulfanilamide. Some German workers consider this compound less toxic than sulfanilamide and curative in 75 to 88 per cent of cases of gonorrhea.[346, 1027]

Clinical results. Papers available for this review noted its effects in gonorrhea but only casually mentioned gonorrheal arthritis. In March 1938, O'Hanlon reported "promising results" with uleron in a few cases of gonorrhea resistant to sulfanilamide. In April O'Mally reviewed a few of the early German papers thereon, and noted his results in 22 cases of gonorrhea including an unstated number of cases of gonorrheal arthritis. The daily dosage was 6 to 8 "tablets" of "uliron" for four days, none for eight days and then a second course (total 20 to 32 gm.). The majority of patients "rapidly improved"; six were unimproved; two were lost sight of. O'Mally approved the German idea of delaying treatment during the first seven or ten days of disease and using adjunct local chemotherapy or vaccines.

Walsh gave "uleron" to 43 gonorrheal patients (none with arthritis): 22 were cured, 21 were not, probably because of the small doses used. However he recommended supplemental local irrigations. As with sulfanilamide there was with uleron the same tendency to early clinical, but delayed bacteriologic, cures. Without giving statistical results from uleron in 150 cases of gonorrhea (arthritis not mentioned) Cokkinis and McElligott stated their inability to agree with the optimism of German workers for this drug. Its ultimate effectiveness in gonorrhea seemed lower than that of sulfanilamide, and to obtain permanent cures several weeks of treatment were necessary. Treating a miscellaneous group of cases including gonorrhea, Bannick, Brown and Foster generally gave daily 60 grains, occasionally 105 grains; total doses varied from 120 grains within two or three days to 1440 grains in 25 days. Resulting blood concentrations averaged only 1.9 mg. per cent.

Toxicity. The drug was tolerated by some patients intolerant to sulfanilamide, and the general incidence of toxicity was low. A few patients noted the following: mild lassitude, headache, anorexia, nausea, malaise, mild cyanosis, skin rashes, vertigo, tinnitus.[49, 724] In one of Walsh's cases gastro-enteritis, fever and giant urticaria developed. Renal and hepatic damage occasionally occur,[846] and one death from uliron was reported in Germany.[1031] Slight methemoglobinemia was noted once but no change in blood cells, no reduction in the carbon dioxide combining power of plasma and no sulfhemoglobin.[49] Although the drug is therapeutically effective and produces few immediate toxic reactions its chief danger is the production of severe peripheral neuritis: five cases were noted by Cokkinis and McElligott, two by Bannick, Brown and Foster, 1 by Van Valkenburg and Von dem Borne, 1 by Wigton and Johnson and eight in Germany.[1031] The drug will produce severe peripheral neuritis in pigeons also.[1031] Hence this drug is no longer used by several workers (Bannick, Brown, Foster; Whitby).

2. Diseptal B. No clinical reports with this compound were noted.

3. Disulon, Diseptal C, Sulfanilyl Sulfanilamide, Disulfanilamide. Two patients with gonorrhea (no arthritis) stubbornly resistant to sulfanilamide were cured by disulfanilamide (Alyea, Daniel and Harris). Disulfanilamide is absorbed more slowly but excreted more rapidly than sulfanilamide;

ethanol sulfanilamide is absorbed and excreted better than either (Marshall, Cutting and Cover). Wigton and Johnson reported three cases of severe peripheral neuritis from "disulon" and "sulfanilyl sulfanilamide."

4. Soluseptasine. O'Hanlon noted no beneficial effect from this drug in cases of gonorrhea resistant to sulfanilamide.

5. Sulfapyridine, 2-Sulfanilamido Pyridine M and B 693. Results with this drug in gonorrhea are, according to Lloyd, Erskine and Johnson, markedly superior to those with sulfanilamide or other sulfonamide compounds. They treated 108 patients with acute gonorrhea (arthritis not mentioned). There were 28 "defaulters." Of the 80 who completed the course of treatment results were "successful" in 85 per cent. Among those cured were some who had gonorrhea resistant to sulfanilamide.

[Results were somewhat difficult to evaluate because some patients were also treated by irrigations.—Ed.]

To 30 patients with genital gonorrhea, six of whom had gonorrhea resistant to sulfanilamide, Bowie gave sulfapyridine daily 45 grains for four to seven days, 20 grains for four to seven days. All patients were bacteriologically cured within one to seventeen days. The drug was considered more rapidly effective than sulfanilamide or benzyl sulfanilamide. Prebble gave sulfapyridine alone (45 grains daily for 5 to 12 days) to 25 gonorrheal patients: 48 per cent were cured, 52 per cent were not. He gave the drug and irrigations to 40 other patients: 63 per cent were cured, 37 per cent were not. Combined therapy was obviously superior (apparently arthritis was not present). Batchelor and his colleagues obtained "over 91 per cent apparent cures" among 102 gonorrheal patients (joints unmentioned) given an average daily dose of 30 to 45 grains for five to six days, then 20 to 30 grains for seven days. Males were cured within seven days, females within fourteen days. Early, not "delayed therapy" was advised.

[These papers give no definite idea of the value of the drug in gonorrheal arthritis. In general the follow-up periods were short.—Ed.]

Toxicity. From experiments on rats, mice and dogs Wien concluded that sulfapyridine is only a fourth as toxic as sulfanilamide. But Marshall, Bratton and Litchfield criticized Wien's work since it was based on the oral administration of poorly absorbed suspensions. From studies based on concentrations in blood they found the drug actually more toxic than sulfanilamide and stated that it should not be used in conditions in which sulfanilamide is generally effective. Toxic reactions were noted in 6,[774] 23 [107] and 29 per cent [55] of patients so treated. They were generally mild, rarely serious (nausea, vomiting, diarrhea, skin rashes, cyanosis, headache, vertigo, methemoglobinemia, fainting, depression, urobilinuria, slight granulocytopenia, and in two cases jaundice). Prebble considered it slightly more toxic than uleron but more effective in gonorrhea. Sulfapyridine is used in smaller doses than sulfanilamide: in comparable doses both are probably equally toxic for man (Lloyd, Erskine and Johnson).

Older Remedies for Gonorrhea and Gonorrheal Arthritis

The following remedies appear to be completely outmoded but some physicians will wish to compare their results with those from the newer remedies. Of Spink and Keefer's 70 cases of gonorrheal arthritis 26 were treated by "medical means" (local chemotherapy, physical therapy, sometimes triple typhoid or gonococcus vaccine): in 20 (77 per cent) of these 26 cases full articular function was restored. Two patients died: one from acute glomerulonephritis, one from pneumonia. In 24 of the 70 cases aspiration of (generally sterile) articular effusions was also "required": normal function of the joints was obtained in 14 (48 per cent). In the remaining 20 cases aspiration of purulent, generally infected, synovial exudates was also required: in only 3 (15 per cent) was complete articular function restored.

Intra-articular injections of rivanol (ethyl oxy-diamino-acridinium hydrochloride) were advocated by Burbacher and Weiland. According to them "acute symptoms are aborted in 60 per cent of acute cases within 48 hours; relief of symptoms is noted in 95 to 98 per cent of all acute cases," generally after only one injection.

[Only one case was reported in detail: data given were insufficient to prove the conclusion to the reader.—Ed.]

For Nonarticular Gonorrhea; Vaccines, Filtrates, Serums, Hormones. Corbus restated the supposed rationale for the serologic control of gonorrheal infections by means of the bouillon filtrate (Corbus-Ferry). Of 24 cases of juvenile vaginitis so treated Goldberg and Blanchard noted cures in 54 per cent. But Scarcello found that such treatment took almost three times as long to produce satisfactory results as sulfanilamide. In Kushner's 36 cases of vaginitis treated by this filtrate it took an average of seven weeks to obtain the first negative smears. Results were "good" in 47 per cent, poor in 53 per cent. Others [130] spoke of the filtrate as having "failed miserably as a cure." Sherman considered a special "antivirus" of value. "Clinical cures" were obtained by 63 per cent of 247 gonorrheal patients given a mixed "antivirus" obtained from broth cultures of mixed organisms found in gonorrheal urethritis; by 44 per cent of 109 patients given a pure "antivirus," and by 67 per cent of 94 patients treated only with local chemotherapy. In the first two groups cures were obtained more rapidly and there were fewer complications than in the last group.

In 1937 Anwyl-Davies reported excellent results in cases of gonorrhea treated by a serum described as a "specific gonococcal antitoxin." The results of others have been very poor. Of 129 cases treated by Burke, Gabe, Harkness and King results were only "fair" in 13 per cent, bad in 87 per cent. Untoward reactions affected 41 per cent, complications, 21 per cent of patients so treated. Use of the serum was considered inadvisable, probably detrimental.

One physician [592] attempted active immunization of women with chronic pelvic gonorrhea by cultures of living gonococcus: 49 (77 per cent) of 63 patients were thus cured. According to Verdier hydrochloric acid is a component part of leukocytes, and when injected intravenously it stimulates and "reinforces" leukocytic activity. He and his associates have given to gonorrheal patients "many thousand injections" generally intravenously, occasionally intramuscularly (each injection 10 c.c. in a dilution of 1:500 HCl). "In no case has there been a failure to achieve curative results. Moreover, there has never been an unfavorable reaction." Brief reports of 25 cases treated by this "new and revolutionary" method were given; "cures" were obtained in every case after four weeks to four months of treatment.

[This report seems very unconvincing to us. The time was long enough for many "cures" to occur spontaneously.—Ed.]

The results of Te Linde in the treatment of juvenile gonococcic vaginitis by estrogenic hormone were excellent. When amniotin was given by mouth or subcutane-

ously in ethylene glycol results were very poor. But cures were obtained in 72 per cent of cases when estrogen in oil was given hypodermically, and in practically 100 per cent of 175 cases when vaginal suppositories (600 international units) of amniotin were given. Good results were also noted by Benson.

Tuberculous Arthritis: General Comments

Clinical Data. The course of tuberculous arthritis can be divided, according to Whitaker, into four phases: 1. During the *period of onset* a tuberculous focus develops in articular bone; this focus may or may not be preceded by one in synovial tissue. 2. During the *destructive phase* articular dissolution tends to occur, general decalcification is always present, and abscesses are sometimes seen. Eventually destruction ceases and the next phase begins imperceptibly. 3. The *quiescent phase* is not characterized by any particular clinical signs. 4. The *period of repair* is characterized by increased bony density, calcification of any bony abscesses present and subsequent bony ankylosis.

[Ankylosis rarely occurs unless the joint is secondarily infected. One of us, A. J. K., has not seen it in a proved case of tuberculous arthritis except in the spine.—Ed.]

Diagnosis. The diagnosis rests chiefly on the development of rather characteristic clinical and roentgenographic features, the latter being more important than the former.[650] Some physicians considered the various accessory skin and conjunctival tests of doubtful value[650]; others considered them useful. In all of the cases finally accepted by Whitaker as tuberculous results of Mantoux tests were positive. A standardized technic is important: negative results are more significant than positive; a condition associated with a repeatedly negative result is nontuberculous. Removal of a piece of articular bone or synovial tissue, examination thereof by microscopy and injection into guinea pigs still remain the only strictly accurate method for early diagnosis. But its routine application to hip joints was abandoned by McMurray because of the risk of permanent sinuses.

Treatment. Prophylactic therapy is of the greatest importance. In Australia most cases are caused by human, not bovine, strains of tubercle bacilli. A definite contact between the patient and a person with open pulmonary tuberculosis was established in 50 per cent of Whitaker's cases. In infantile tuberculous arthritis contact was almost always between the infant and a "parent just home from a sanatorium." Such contacts must be prevented by public health authorities.

Since tuberculous arthritis is merely a local manifestation of a constitutional disease its treatment must be (1) constitutional and (2) local. Fundamental features of constitutional therapy include rest, fresh air, sunlight, diet therapy, and removal of septic foci.[204, 1025] Artificial stimulation of bodily resistance was considered valueless (Whitaker). According to Colvin, adequate constitutional treatment cannot be obtained in general hos-

pitals, but only at special open-air hospitals where proper constitutional and local therapy can be combined. Recently physicians have expressed a growing conservatism as to whether the most successful local therapy involves use of surgical or nonsurgical procedures. Current reports again indicate an increased appreciation of the value of conservative, i.e., nonsurgical, methods.

Cases of tuberculous arthritis at any stage were not considered suitable for hydrologic spa therapy,[954] or for synovectomy.[482]

Tuberculous Arthritis; Special Localizations

Tuberculous arthritis more commonly affects lower extremities of children, upper extremities of adults. Involvement of upper extremities is about seven to nine times less common than that of lower extremities but is more severe and destructive (Steindler).

Shoulder. Tuberculous arthritis of a shoulder is rare; it affects adults (generally aged 40 to 50 years) four times as often as children. The synovial bursa of the biceps is a common primary source of infection. Steindler recognized two types: (1) a fungus synovial type present in 25 per cent of cases and (2) a primary osseous type. The latter was subdivided into (*a*) caries sicca and (*b*) fungus osseous type. The caries sicca type of tuberculous arthritis was the more common, and was characterized by dry destruction of cartilage and subchondral bone, atrophy of adjacent muscles, no articular swelling, a tendency to slow spontaneous fibrous ankylosis. Because of the last, end results were more favorable. The fungus osseous type was associated with granulomatous proliferation, marked swelling, abscesses (in a third of cases) and sinus formation. Its treatment is more difficult. Incision and drainage of abscesses give only temporary improvement. Resection is indicated occasionally, but operative fusion is generally necessary (with the arm in position of about 30 to 50 degrees abduction and forward flexion), and usually results in solid fusion of a painless joint with a fair range of motion of the shoulder at acromioclavicular and sternoclavicular joints.

Elbow. Tuberculosis of this joint is not uncommon and affects two adults to one child. Steindler recognized types and subtypes as in tuberculosis of shoulders, and noted abscesses in a third of his cases. Healing with full mobility occasionally occurred, more often in children than in adults; hence conservative treatment (long immobilization until the disease becomes inactive, then mobilization) is more applicable to the former. Surgical treatment is generally necessary. Arthrotomy is usually inadequate. Fairly early fusion of the joint in a suitable position gives best results.[909]

Wrist. This joint is affected more often than shoulders, less often than elbows, more often in adults than children. It is commonly associated with tuberculosis of adjacent flexor tendons and of lungs. Surgical therapy is indicated if roentgenograms indicate progression of the disease after two

or three months' immobilization of the wrist in a plaster splint. Total resection was considered superior to partial resection. Incision and drainage were considered useless, amputation rarely indicated.

[By some, early arthrodesis is considered the best.—Ed.]

In tuberculosis of joints of upper extremities, Steindler considered results of surgical treatment superior to those of conservative therapy.

Knee. In treating tuberculous arthritis of a knee joint by arthrodesis the patella offers a practical source from which a bone graft may be obtained. Meng described a new method for this procedure.

Spine. A careful "unprejudiced" 10 year test was made by Finkelstein, Greenberg, Jahss and Mayer to determine the relative value of surgical and conservative treatment of tuberculous spondylitis, to answer specifically the question: "Does the [fusion] operation shorten the course of the disease and prevent deformity?" One group of 26 patients was treated by fusion (Kleinberg method once, Hibbs method three times, otherwise the Albee method). The other group (17 patients) received "purely conservative measures" (complete rest on frames or plaster shells, the best of food, sunlight, fresh air, and in a few cases special measures such as tuberculin therapy, liver meal, splenic extracts, etc.). The two groups were closely parallel as to age of patients, duration, severity and location of disease. Strict criteria of "cure" were laid down. The surgical group required 40 per cent *more* time (average 1215 days) for their cure than the nonsurgical group (average 876 days). Apparently fusion operations prolonged, rather than shortened, the course of the disease. Despite firm fusions the pathologic process in the vertebrae themselves was apparently uninfluenced. Abscesses developed in 20 per cent of the surgical, in 18 per cent of the other group. Operation did not prevent paraplegia which occurred in four cases of each group. In spite of "successful fusion" recurrences occurred. Spinal deformity appeared to progress equally in both groups.

In conclusion the investigators were "impressed not only by the ineffectiveness of the fusion operation but by our ineffectiveness as physicians. An average of 876 days of care for patients not operated on is a high figure" which confirms experiences of others and shows how little can be done to hasten healing. "We are compelled to admit that tuberculosis of the spine is a chronic disease which runs its course, little influenced by the efforts of the orthopedic surgeon. This should act as an incentive to the development of more effective methods of treatment."

[These results are contrary to the experience of one of us, A. J. K. Further studies on this problem are needed.—Ed.]

Hips. Location of the primary articular tuberculous focus in 82 cases of tuberculous hips was noted by Hatcher and Phemister. The disease began in childhood in 70 cases, in adult life in 12 cases. Of children, the primary focus was in the neck of the femur in 14 cases, in the ilium in 10, in the ischium in 2, unlocated in 44. In no case was it in the head (epiphysis) of the femur. In other hematogenous infections also the femoral

capital epiphysis seems to be immune as a site of primary focus; this immunity seems to be dependent on the blood supply of the femoral head. The primary focus of the 12 adults was in a greater trochanter in two cases, in the ilium in one, unlocated in nine.

Tuberculous hips are uncommon in Australia, especially in South Australia where there have been less than 100 cases in 20 years (Betts).

Details of treatment were reviewed (Betts; Colvin; McMurray; Whitaker). The essence of treatment is complete, uninterrupted, prolonged fixation of the joint by surgical or nonsurgical means, fixation being continued until the disease becomes clinically and roentgenographically inactive. Articular destruction results chiefly from increased intra-articular pressure due to weight bearing and muscle spasm. [Is not articular destruction due to erosion of bone by tuberculous granulation tissue?—Ed.] These factors can be corrected by treating the patient in recumbency and relaxing muscle spasm by complete articular fixation. The method of fixation chosen may vary. Current writers unanimously favored prolonged trial of nonsurgical methods and the use of surgical operations only late in the disease when conservative therapy had failed definitely.

[One of us still believes that early surgical fusion of tuberculous hips is generally indicated.—Ed.]

For nonsurgical fixation the splint or frame used must be rigid enough to fix the joint but must permit access of sun and air to the joint, application of dressings to sinuses, and general nursing care without alteration of the joint's position. During the period of treatment in recumbency use of a Jones abduction frame was favored by Betts, Colvin, and McMurray; a bivalved plaster spica with subsequent use of a Bradford frame was favored by Whitaker. Colvin also used traction. Time required for treatment in recumbency varied from 1.5 to 2 or 3 years in McMurray's cases. Evidences of inactivity of the disease are absence of fever, pain and formation of abscesses, improved general health, and bony recalcification.[650] When the disease becomes inactive ambulatory therapy is indicated. Fibrous ankylosis generally results unless secondary infection occurs, in which case bony ankylosis may ensue. If the latter occurs, no external support may be necessary during "ambulatory treatment." Otherwise some external support is generally required unless the presence of short, stout, wide, fibrous ankylosis has produced as "sound" an ankylosis as a bony one. Some physicians used plaster, a leather case or single Thomas splint[650]; others used a walking spica or a double Thomas splint.[82, 1025] Such conservative ambulatory treatment should be continued for at least 18 months. If a sound ankylosis has not occurred, then and only then should surgical methods be considered. The likelihood of a sound or unsound ankylosis can be predicted by certain roentgenographic features.[650] Conservative therapy has been reported to produce sound ankylosis in hips in "at least 70 per cent of patients,"[650] and in "the majority" of cases.[82, 204]

The following results from conservative therapy were noted. In Col-

vin's series successful results were obtained in 21 per cent of cases with sinuses antedating treatment, and in 58 per cent of those without sinuses. Sound ankylosis resulted in 22 of Betts' 31 cases. Whitaker obtained bony ankylosis in 40 per cent, "presumptive ankylosis" in 55 per cent, no ankylosis in 5 per cent. The disease lasted an average of at least five or six years. Disadvantages of conservative therapy are that it is costly in time and money and is occasionally ineffective.

[Unfortunately some tuberculous hips "soundly ankylosed" by fibrous tissue flare up later and require arthrodesis.—Ed.]

Surgical procedures in vogue are (1) intra-articular arthrodesis ("generally unsatisfactory") [650]; (2) extra-articular arthrodesis; "more satisfactory"; (3) the combined method (preferred by McMurray); (4) production of a pseudarthrosis (valuable for elderly patients); (5) corrective operations, e.g., various forms of osteotomy (preferred by Betts). There is no urgency in the matter of surgery.[204] Sometimes a "successful" early fusion operation may be actually harmful by retarding collapse and closure of the bony cavity produced by osseous destruction. Disadvantages of surgical therapy are that there are definite chances for death therefrom or for secondary infection, sinus formation or unsuccessful fixation thereafter. "Operation does not help to control or diminish joint dissolution" (Whitaker).

[In this some of us do not agree.—Ed.]

Tuberculous Rheumatism

According to Najib-Farah genuine acute rheumatism (i.e., rheumatic fever) and Poncet's tuberculous rheumatism are often mistaken for each other. In five "typical cases" of Poncet's rheumatism the plasma bilirubin concentrations varied between 0.1 and 0.3 mg. per cent; in "genuine acute rheumatism" the concentrations were always higher, a point of diagnostic significance.

[These are very low figures for plasma bilirubin; the method used for their estimation was not stated. No clinical data were given to clarify the supposed entity of tuberculous rheumatism, one not accepted in the United States.—Ed.]

Pneumococcal Arthritis

Pneumococcal arthritis is rare,[5] and will probably become rarer if the promising results from use of the newer sulfonamide compounds are confirmed. No cases of pneumococcal arthritis were noted among the numerous cases of pneumococcal infections treated recently with sulfanilamide or sulfapyridine.

Earlier reports [5] indicated that sulfanilamide had slight but definite pneumococcocidal properties. In some cases the drug favorably affected experimental pneumonia (types I and III), human pneumonia (especially type III), pneumococcal meningitis and brain abscess (type V), septicemia (type II), and otitis media (type III). But in other instances similar conditions were not benefited. Further results with sulf-

anilamide have been generally disappointing. Beneficial effects have been ascribed to the drug in the treatment of experimental pneumonia (types III and VII),[209] experimental pneumococcic meningitis (types I and III),[544] human pneumonia (types I to IX) [116, 737, 794, 824, 1036]; but especially in treatment of the usually fatal pneumococcic meningitis. Recovery in 14 cases of the last disease (from various types of pneumococci) was reported.[21, 33, 313, 1055] Some physicians noted no effect in other cases of pneumonia [116] and pneumococcic meningitis.[913] Long and his colleagues [298] considered sulfanilamide of little value in pneumococcic pneumonia but somewhat effective in type IV pneumococcic meningitis. Osgood [737] noted that the drug had a slight inhibitory effect on pneumococci (types I, II, III and VIII) in human bone marrow cultures but not as much as small doses of serum. Sulfanilamide and serum combined had an effect superior to either alone. No justification was found for the use of sulfanilamide alone in human pneumonia. The effects of disulon, uleron, and septasine on experimental pneumonia (types I and III) in mice were insignificant; that of diamino diphenylsulfone was very definite but the drug is too toxic for humans.[298]

Much more striking have been the effects of sulfapyridine. Whitby showed that the drug possessed great activity against pneumococci and experimental pneumococcic infections of several types, especially types I, VII and VIII, less notably types II, III and V. Rapid recovery following use of the drug was noted in many cases of lobar pneumonia from various types of pneumococci,[260, 291, 322, 947] and in pneumococcic meningitis [797] and septicemia.[259] Evans and Gaisford noted a reduction of mortality from 27 per cent of 100 cases of pneumonia treated otherwise to 8 per cent of 100 cases treated with sulfapyridine. The drug causes degeneration of the capsule of the pneumococci and resulting loss of their type specificity.

Syphilitic Arthritis and Synovitis: Charcot (Tabetic) Joints

The various ways in which syphilis may affect muscles, joints and related structures were briefly reviewed and the commoner types were discussed in some detail.[640, 701, 703, 879]

1. Arthralgia. This affects 5 to 10 per cent of patients with early syphilis. Pain arises from an unknown cause, perhaps from mild juxta-articular periostitis. Among 8000 consecutive cases of syphilis studied by New and Brittingham were 61 (0.76 per cent) of "inflammation of joints." Pain affected one joint in 7 cases, multiple joints in 54 cases, and was quickly relieved by two or three injections of neoarsphenamine. Severe joint pain was present but no bony changes, no case of Charcot joint and only one case with hydrops (knee). "Whether such *inflammation* is a true arthritis or merely an arthralgia is not important."

[We cannot agree to this statement. Not enough details were given for one to conclude what type of articular disease was present.—Ed.]

2. Syphilitic Synovitis or Arthritis. This occurs in only 1 per cent of cases of early syphilis, more often in late syphilis. The commonest variety is "Clutton's joint," bilateral synovitis with hydrops of knees in a congenital syphilitic. It is characterized by marked swelling, slight heat, pain and tenderness, no redness and no bony changes even though the condition may persist for years. The cellular content of synovial fluid is not characteristic; total synovial leukocytes number 10,000 to 45,000, and relative lymphocytosis is present (McEwen and Thomas).

Synovitis may also affect patients with acquired syphilis. Synovectomy was considered very useful (Swett).

[To us synovectomy in such cases seems unwise and unnecessary since antisyphilitic treatment is generally promptly effective.—Ed.]

Syphilitic polyarthritis may occasionally occur.[640] Diagnosis is based on the clinical features, lack of response to antirheumatic measures, positive Wassermann reaction, and prompt response to antisyphilitic therapy.

3. Gummatous Arthritis. This occurs only in tertiary syphilis. Roentgenograms may reveal large or small gummatous areas of destruction and sometimes secondary osteo-arthritis. An illustrative case was described.[640] According to Smith[879] this type "may often assume the characteristics of rheumatoid arthritis with fusiform swelling of fingers, pain, intermittent temperature with exacerbations and remissions. It may so closely resemble chronic rheumatoid arthritis as to justify serological study of all cases so diagnosed." But McEwen and Thomas never saw a case of syphilitic arthritis in which differentiation from rheumatoid arthritis was difficult.

[Our experience coincides with that of McEwen and Thomas. Nonarticular syphilis and atrophic arthritis may occasionally coexist.—Ed.]

4. Periostitis Adjacent to Joints. This may cause arthralgia. An illustrative case was described.[640]

5. Charcot Joint, Tabetic Osteo-Arthropathy. This affects about 4 per cent of tabetics; in 75 per cent of cases joints of lower extremities are affected. The usual features were described: slow or sudden onset of articular swelling and instability, effusions present or absent, variable degrees of joint destruction, characteristic roentgenographic and neurologic abnormalities. [The joints are generally painless, occasionally even anesthetic, but sometimes somewhat painful.—Ed.] The condition may progress slowly or rapidly. Its exact pathogenesis is unknown. Seven new cases were reported.[181, 640, 658, 792, 1050] That of Menninger and Carlson was very unusual: a case of congenital syphilis in a 60 year old woman who at the age of 43 years began to develop multiple tabetic arthropathies (a hip, a lumbar vertebra).

The treatment of Charcot joints is usually unsatisfactory. Antisyphilitic therapy is not effective. Mechanical supports are generally prescribed. McEwen and Thomas reported some success with fusion operations in cases with little articular destruction. Operation too often fails to provide a stiff joint. An improved technic for arthrodesis of Charcot joints was described by Soto-Hall: multiple bone drillings of involved articular bones to improve vascularity and osteogenesis; immobilization for four to six weeks by a posterior plaster splint; then a standard arthrodesis.

[This appears to be a procedure worthy of more extended trial.—Ed.]

Fever therapy does not affect Charcot joints but may be a prophylactic measure as it may favorably affect cases of early or late neurosyphilis. Several references will interest those concerned with the present status of fever therapy for syphilis.[72, 74, 474, 647, 709, 735, 751, 837, 885]

6. Rarer Forms. Some rarer, less certain forms of supposed syphilitic rheumatism were noted,[879] including that of a young woman with severe syphilitic osteolytic lesions of bones, especially radius and ulna, severe tenderness and pain in muscles, bones and joints, and extreme muscle atrophy; antisyphilitic treatment rapidly relieved the symptoms (Newman and Saunders).

Brucellosis, Undulant (Malta) Fever

Incidence. From 1930 to 1937 inclusive 14,938 cases of brucellosis with 597 deaths therefrom were reported in the United States (2,497 cases with 58 deaths in 1937). Yearly figures were reported for each state. "The total number of cases actually occurring is undoubtedly much larger than that reported." These totals, published by the United States Public Health Service [976] are slightly higher than the unofficial totals collected by physicians and reported in previous Reviews. Studies on the incidence of the disease were also reported from Connecticut,[957] Pennsylvania,[320, 321] Vancouver,[251] England,[235] Scotland,[61, 62] Malta,[349] and Egypt.[61, 537, 1056]

Clinical Data. Several short general reviews of the subject appeared.[164, 235, 289, 748] The incubation period of the disease varies from one week to not less than four months (Hardy, Frant and Kroll). The new cases illustrated again the protean symptoms of the disease. Commonest symptoms were fever of varying severity and duration, chilliness, fatigue, weakness, sweating, malaise, headache and generalized aching. Any of these symptoms can be dominant, with others slight or absent. Leukopenia generally is present, occasionally leukocytosis, with relative monocytosis. Because of the vague general symptoms the disease, when acute, is commonly misdiagnosed as influenza, or when chronic, neurasthenia or tuberculosis. Sometimes the disease produces more discrete symptoms: pneumonia, meningitis, iritis.[94, 795] Postmortem studies are of interest because they are rare: those in two cases were reported.[94, 655]

Symptoms Referable to Muscles and Joints. As previously, certain writers [369, 370, 946, 795] have again stressed the frequency of actual arthritis (acute or chronic) as a common feature of brucellosis, but a careful review of current reports leads to the conclusion that a true arthritis rarely occurs although arthralgia and myalgia are common symptoms. Of the Abbotts' 11 patients seven had general aching, backache and neckache and one "extreme joint pains." Two authorities (Evans [289]; Dalrymple-Champneys) noted "joint pains" and "pains in limbs" not infrequently but did not mention true arthritis as a feature. Patients with "pains in back and joints," [343] "muscle and joint pains," [251, 655] "cramp-like pains in muscles of arms and legs," [777] "severe joint pains" (in one of 28 cases),[290] "sciatica" (in one of 20 cases),[708] and "rheumatic pains in joints" [707, 708] were noted. But these were not constant features and many patients apparently experienced no joint or muscle pains.[320, 321, 749] A previous diagnosis of "rheumatic fever" in one case and "septic arthritis" in another became obviously un-

tenable to Dolman. Arthritis was a major complaint in 12 of the 100 cases of Schmidt and Dorsey (Oklahoma). In a few of the cases of Passarelli and Sloan "inflammatory joints" were noted: "General muscle and joint pains are common, and joint involvement resembling that of rheumatic fever is not uncommon." But they are not definitely responsive to salicylates. Newman [705, 707] himself had "probable undulant fever"; for the next 20 years he suffered periodically from attacks of muscle, joint and nerve pain which affected a sciatic nerve, a shoulder, sometimes many joints. Attacks of pain and stiffness recurred for two to three days every three to four weeks, were unrelieved by removal of foci, but relieved when at long last treatment for brucellosis was begun. "If the physician will round up his chronic complainers and neurotics, especially those complaining of neuralgia and arthralgia, and apply modern methods of diagnosis he will be shocked to find how many really have the disease [brucellosis]." [707]

[In some such cases of myalgia, arthralgia and fatigue a diagnosis of "primary fibrositis" might be entertained, but the differentiation should not be difficult. In primary fibrositis there is no fever, no characteristic leukopenia, and the sedimentation rate is practically always normal. In brucellosis there is usually some fever and sedimentation rates are generally abnormal.—Ed.]

That brucellosis commonly masquerades as chronic atrophic arthritis is the idea again expressed by a few physicians in the Southwest. Thus McIntire (Texas) wrote: "Brucellosis is one of the many causes of chronic arthritis. Two patients reported who had rather extensive atrophic arthritis with complicating hypertrophic changes. Both patients had strongly positive tests for brucellosis; both were extremely sensitive to the intracutaneous test." [It is likely the arthritis was quite unrelated to the brucellosis. No evidence was given that the arthritis responded to antibrucellosis therapy.—Ed.] Reed and Goldfain noted five patients with recurrent iritis, three of whom had rheumatic symptoms, the syndrome being due presumably to brucellosis. [Iritis sometimes complicates cases of atrophic arthritis.—Ed.] One patient had "Marie-Strumpell spondylitis" with irritation of an eyeball recurring "since he began to have his serious symptoms of arthritis." Another patient had recurrent lumbago and iritis; a skin test for brucellosis provoked both complaints. Another patient had muscle and joint aches, fever, malaise and iritis, later "subacute synovitis" of a knee and ankle. In all these cases laboratory tests indicated the presence of brucellosis. In the last case the arthritic symptoms disappeared, once under nonspecific therapy, later after specific vaccine therapy for brucellosis.

Fifty cases of "apparent rheumatic and arthritic disease" were tested by Goldfain [370] (Oklahoma) for brucellosis. [The terms "rheumatic and arthritic" seem to have been used rather liberally as among the 50 cases there were six of "psychasthenia" or "psychoneurosis" and one of "chronic choroiditis." These are not "rheumatic diseases." There were 19 of "atrophic arthritis," 10 of "hypertrophic arthritis," 8 of "fibrositis," 3 of "psychoneurosis or psychasthenia and fibrositis," 2 of "sciatica," one of "ankylosing spondylitis."—Ed.] Fourteen patients gave "positive agglutination tests" (titers unstated); 36 had positive

reactions to skin tests of mild to severe degree; mild to marked opsonophagocytic activity of blood was present in all cases. It was concluded that 31 of these patients with apparent rheumatism actually had "active brucellosis in addition to other diagnoses." Arthralgia was present in all 31 cases, backache in 90 per cent, neuritis and neuralgia in 48 per cent, myositis in 32 per cent, spondylitis in 6 per cent, "persistent joint stiffness" in 26 per cent. It was inferred that these symptoms were expressions of the brucellosis. In another group of 157 patients "the great preponderance of whom were suffering with rheumatic disease" (apparently 80) 51 per cent were given a diagnosis of brucellosis by Goldfain [369] on the basis of similar laboratory tests. Of 23 patients adequately treated with Brucella bacterin 90 per cent were improved or cured. Admittedly results may have been due to nonspecific protein therapy.

[These reports have failed to prove that the rheumatic symptoms were actually due to brucellosis, or for that matter, that active clinical brucellosis was present. Apparently in the Southwest, especially Oklahoma, latent brucellosis is quite common. Perhaps a similar number of patients with any chronic disease might show a similar percentage with "positive" results to tests for brucellosis. Either the Oklahoma strains of Brucella are peculiarly arthrotropic or these cases represent the coincidental relationship of chronic rheumatism and latent (unrelated) brucellosis. In the light of most reports we are not convinced that true acute or chronic arthritis is commonly due to brucellosis. Previous Reviews have noted rare bona fide cases of specific joint and muscle lesions from brucellosis.—Ed.]

Diagnosis. The significance of laboratory methods used to confirm the clinical diagnosis was again discussed. Opinions differed as to which of several tests is the most reliable.

Agglutination Tests. In the University of Pennsylvania Hospital and in the Cook County Hospital, Chicago, a titer of 1:80 or over is considered positive.[320, 748] A positive agglutination reaction in dilution of 1:40 or higher was considered the most reliable sign of infection by Evans, Robinson and Baumgartner. A reaction at this titer does not often occur in cases with no history of brucellosis. [At The Mayo Clinic titers below 1:160 are usually not considered significant; in all cases titers must be interpreted in connection with clinical data.—Ed.] Agglutination reactions at a titer of 1:40 were obtained for 3.2 per cent, of 1:80 for 1.6 per cent of 316 persons ill with other diseases, for none of 26 healthy subjects.[290] Of 5000 blood serums routinely submitted for Wassermann tests in a general hospital (Denver) 51 showed brucellosis agglutinins at titers of 1:25, 9 of 1:100, a total of only 60 or 1.2 per cent.[352] Of 170 apparently healthy children none had positive reactions (titers 1:20 to 1:100).[571] But a negative reaction (i.e., a titer below 1:40) does not prove the absence of the disease; almost half of the chronic cases react negatively.[290] Furthermore, in acute cases the test may not become positive until after three weeks of disease.[235] Infected guinea-pigs show agglutinins the ninth day.[149] An improved technic, using stained antigens, was reported.[668]

Skin Tests. These were considered the most reliable by some [320, 436, 524, 646] but less reliable than agglutination tests by others.[290] In one series positive skin reactions were found in 93 per cent of patients who had had brucellosis, in 61 per cent of those with chronic brucellosis, in 14 per cent of persons sick otherwise and in 11 per cent of healthy persons.[290] False positive reactions occur not infrequently (in 18 per cent) among tuberculous children.[571] Among 491 patients in a general hospital 12 per cent

had positive reactions.[352] Tests with heat-killed vaccine produce more severe reactions than those with brucellergin. Using the latter, positive reactions were found in 9 per cent of 7122 Kansas City school children; the percentage incidence of positive tests increased with age.[81]

Opsonophagocytic Test. Evans[288] found this test practical but one to be interpreted carefully. But she and her colleagues[290] found it the least reliable of the specific tests because of frequent false-positive results (weakly positive in 22 per cent, strongly positive in 9 per cent) among persons ill of other diseases. Because they found strong positive reactions in cases of chronic brucellosis and weak or moderate reactions after recovery they could not confirm the opinion of others that strong reactions indicate immunity and weak reactions indicate infection. In this opinion Keller, Pharris and Gaub concurred. Cain described an improved stain technic for the test.

Clinical and animal experiments by Welch, Wentworth and Mickle indicated that sulfanilamide markedly increases opsonophagocytic activity for Brucella organisms. In animals the average percentage of cells showing marked phagocytosis before treatment with sulfanilamide was 20, after treatment 97. Curiously also, in three of five human cases of brucellosis agglutination tests gave negative results before administration of sulfanilamide and positive results afterward.

Cultures. "There is no reliable test to detect chronic brucellosis. Brucella infections occur in which all three specific tests give negative results. The only proof of brucellosis is the cultivation of the organism—a difficult and time consuming procedure" (Evans, Robinson and Baumgartner). In this connection the case of chronic brucellosis of 25 months' duration studied until death by Menefee and Poston is of great interest. Repeated skin, agglutination, and opsonophagocytic tests gave negative results. Cultures of blood, urine, stool and sputum were also negative for Brucella organisms but *Brucella suis* was isolated before death from enlarged lymph nodes and the gall-bladder, and after death from liver, spleen, testes and numerous lymph nodes. Poston described methods used in obtaining cultures.

[This case suggests that if one has good clinical grounds for a diagnosis of brucellosis unsupported by the usual laboratory tests, biopsy and culture of lymph nodes (if enlarged) are indicated.—Ed.]

Treatment of Brucellosis

Serums and "Specific" Vaccines. Five patients, ill from 1 to 13 months, were given polyvalent antimelitensis serum from cattle immunized to *Bacillus abortus* and *melitensis*; all five made a complete recovery within three weeks and remained well (Flippin).[321] Results with Foshay's serum and vaccine seemed "excellent" to Newman[705] in January, "encouraging but not perfect" 11 months later.[707] [No details were given.—Ed.] McIntire considered Brucellin, a filtrate of a broth culture of Brucella organisms, superior to Foshay's and other vaccines. Others were not impressed with the value of serums and vaccines.[6, 436, 748]

Typhoid Vaccine. Fever reactions with typhoid vaccine seemed useful in two cases of Herndon and three of Etter.

Fever Therapy. This therapy gave Newman[705] "encouraging results" (no details). In two acute cases so treated recovery was prompt, but relapse occurred in one.[707] Of nine patients of Prickman, Bennett and Krusen, seven were cured after 5 to 22 hours of artificial fever. Similar cures were noted in 8 of 9 unpublished cases treated by others, and in 2 of 3 published

cases: a total of 17 cures (81 per cent) in 21 cases. Fever therapy must activate man's protective mechanism against the germs since sustained temperatures of 107° F. do not kill *Brucella abortus* in vitro.

Chemotherapy. The Abbotts gave from 2 to 13 intravenous injections of metaphen (each 10 c.c. of a 1:1000 dilution) in 10 cases; "in most of them there was a relatively prompt decline in temperature and improvement in symptoms." Fouadin (trivalent antimony compound) "cured" one patient (Thomson)[953] but not two others (Manson-Bahr; Punch).

Sulfanilamide appears to be the most promising remedy. Striking recoveries followed its use in eight cases treated in Europe during 1936 to 1937 (listed by Blumgart). Analysis of some of these reports suggests that the patient may have been entering a period of remission or recovery when treatment was begun (Sheppe). But even so, further experience seems to indicate that the drug is truly effective. Twenty reports during 1938 gave results from sulfanilamide in 60 cases of acute and chronic brucellosis: 52 (87 per cent) were "cured," generally promptly within four to seven days. The largest series of cases (20) was that of Newmann. He first gave prontosil intramuscularly (5 c.c. on alternate days) to four patients. None was benefited, probably because the doses were small. Then to 16 patients he gave sulfanilamide orally (to children four "tablets," to adults six "tablets") daily for eight or more days: 15 were cured in from 2 to 20 (average 7) days; only one failed to respond. The only other failures were in 2 cases of Herndon in which small doses were given, and in one case of O'Reilly in which only 90 grains in four days were used. Cures were reported in five cases each by some,[343, 953, 1019] in three each by others,[617, 910] in two each by others,[330, 331, 803, 961] and in one case each by several.[99, 398, 406, 585, 586, 781, 858, 958] In most cases sulfanilamide was used alone in oral doses ranging from 60 or 75 grains daily for about nine days to 35 grains daily for about ten days. Several physicians prescribed 60 grains daily for seven to ten days. The use of fairly large doses was advocated by Stern and Blake and by Welch, Wentworth and Mickle (e.g., daily dose: 90 grains for five days, 120 grains for five, 60 grains for three). But rapid results were sometimes noted from smaller doses: fever disappeared within 36 hours in a case after administration of 105 grains (Stern and Blake); a patient of Traut and Logan, critically ill, jaundiced and in stupor, was given a transfusion, and 30 grains of sulfanilamide daily, and became afebrile in 48 hours. The combination of sulfanilamide (oral) and prontosil soluble (subcutaneous) was used by some.[331, 406, 781, 803] Usually only one course of medication was required; occasionally relapses occurred but prompt response followed a second course.[343, 803] Hence some[803, 953] recommended the routine use of one to three follow-up courses, each a week long, within two or three months of the "cure."

Studies by Francis suggested that *Brucella abortus* in vitro is much more susceptible to sulfanilamide than *Streptococcus pyogenes.* That the drug seems to increase opsonophagocytic activity markedly has been mentioned.[1019]

"Prosepticine" (benzyl sulfanilamide: 0.75 to 1.5 gm. daily for seven days) was used by Bevan to cure one case in a child 5½ years old.

Prophylaxis. Any solution of the problem of undulant fever which protects man but ignores the vast economic problem of Bang's disease in cattle is but a makeshift remedy. Universal pasteurization is an artificial barrier, not always practicable and won't be attained in our lifetime (Anderson).[28] Measures to prevent the spread of the disease among cattle and to protect dairymen, butchers and veterinarians were discussed.[28, 349, 706] The disease can be spread, not only by unpasteurized milk, but by butter, cheese and ice cream made from such milk.[748]

Typhoid Arthritis: "Typhoid Spine"

Typhoidal involvement of the spine is said to occur only once in 1800 cases of typhoid fever. It is now quite rare. Swart reported a case in which osteitis developed rather than an osteomyelitis: destruction of the intervertebral disk between the second and third lumbar vertebrae, and the adjacent borders of the vertebral bodies. Spinal symptoms began two months after the onset of typhoid fever, one month after convalescence therefrom. Recovery was expedited by traction in hyperextension on a convex frame; later a hyperextension cast, then a Taylor brace were used. Supports were discarded at the end of eight months; the patient "was apparently completely well in one year."

Meningococcic Arthritis

An interesting synopsis of the literature on this condition from the time of Welch (1810) was presented by Schein who reported 23 new cases. The incidence of articular lesions in meningococcic infections has varied from 4.8 to 20 per cent in different epidemics; it was recently 7.7 per cent at Bellevue Hospital. Articular lesions were classified thus: (1) an early, often premeningitic, polyarthritic or arthralgic form; (2) the usual postmeningitic monarticular form; (3) a type resembling serum sickness and (4) occasional postmeningitic spondylitis. Intermediary and atypical forms abound.

Type 1. In these cases the mortality is high but there is scant articular involvement. When it does occur, it may be in the form of polyarthritis or polyarthralgia resembling rheumatic fever or gonorrheal "rheumatism." It occurs either during the first few days of the general infection or may antedate it. If the latter occurs, diagnosis is especially difficult. Joint symptoms are often transient and are due to periarticular and intra-articular petechial hemorrhages. Symptoms may include severe pain, marked redness, tenderness and spasm; swelling is slight or absent. It is associated often with a severe hemorrhagic skin rash and a fulminating severe infection. The general prognosis is poor; that of joints is good.

Type 2. The usual type is that of true meningococcic arthritis with gross articular damage. One joint is usually affected alone or dominantly. Symptoms appear occasionally with, or one or two days before, the onset of the general infection, but they usually appear after the fifth day of the general infection. There is usually a

marked purulent articular effusion in which meningococci are often found, but there is relatively little pain, redness, tenderness or spasm. Synovial fluid contains excess polymorphonuclears and protein. In this type the general disease is less severe and the mortality lower than in type 1; the general prognosis is good but that for the affected joint is poor. Contrary to previous observers Schein frequently noted irreparable articular damage in adults, but not in children under 12 years of age.

Type 3. Included are cases of mild articular involvement due to or resembling serum sickness. Symptoms appear after the sixth day of the general disease, and one or several joints are affected with serous arthritis; cultures of joints are negative. Pain, redness, swelling, tenderness and spasm are all moderate. There may be an urticarial or erythematous skin reaction. If this type of meningococcic arthritis occurs in the second week of disease about the time when serum sickness frequently occurs, differentiation is difficult but not particularly important because either type of articular reaction (type 3 or serum sickness) is fairly mild and the prognosis excellent. Schein concluded that most cases of this type are from the disease, not the serum.

Type 4 (?). A few cases of "post-meningitic spondylitis" have been reported: localized osteo-arthritic lesions affecting two adjacent vertebral bodies and their intervening disk. They may represent a true meningococcal entity, but Schein suspected that some such cases result from damage to disks from repeated spinal punctures.

In the usual (type 2) form the site of involvement in Schein's cases was knee in nine, hand in seven, elbow in six, wrist in five, ankle in four, hip in three, and tarsus in one case. Marked destruction affected two elbows, two hips, a wrist and a knee. Death, unrelated to joints, occurred in three of the 23 cases.

Among 191 cases of meningococcic meningitis seen by Bolduan were 16 of "arthritis" (no details). In Corbett's case of meningitis (of unidentified bacterial type) hands, ankles and wrist were swollen and painful. Many joints were affected mildly in Lambie's case of meningococcal bacteremia.

Treatment. Schein treated the general infection by serum, and recommended the use of Hoyne's antitoxic antiserum as a remedy which lowered the incidence of complications, including arthritis. Articular lesions were treated by aspiration, splinting, occasionally traction.

Sulfanilamide. Further reports testify to the "profound effect" which sulfanilamide has on meningococcic infections. Among 205 cases of meningococcic meningitis (none with arthritis) cited and treated by sulfanilamide alone [48, 66, 85, 116, 228, 515, 677, 913, 1037] or in combination with serum,[30, 85, 112, 116, 486, 497, 677, 681, 712, 884] there were only 17 deaths. Whether the drug was used alone or not, recoveries were generally prompt and complete, rapid sterilization being accomplished. The following figures indicate that sulfanilamide is as effective, indeed perhaps more effective than serum: Of 75 patients treated by Stevens with serum 43 per cent died; of 17 patients given the drug, only 18 per cent died. Banks noted the death of 16 per cent of 38 patients given serum alone, of 12 per cent of 59 given serum and sulfanilamide, of 6 per cent of 60 given the drug alone. Smith, Maxson and Murphey noted a reduction of mortality from 41 to 13 per cent when the two remedies were used rather than antitoxin alone. Some physicians con-

cluded the combined therapy (drug and serum or antitoxin) was superior to the use of either alone; others concluded that sulfanilamide could be used alone with confidence in all but the most serious cases. Some gave the drug orally, subcutaneously and intrathecally in varying doses according to the severity of the disease. Others insisted it was not necessary to give it intrathecally, perhaps not even subcutaneously, the oral use being sufficient.[681, 1037] One of Willien's patients who failed to recover with $500.00 worth of serum given in 41 days was cured in 14 days by the use of $2.00 worth of sulfanilamide.

Further studies on the inhibiting effect of the drug on meningococci in vitro [699, 700] and on experimental infections [293] were reported.

Persons in attendance on patients having meningococcic infections seemed to be protected by taking 45 grains of the drug daily for six days (Bickel). Some recommended that it should also be given to carriers.[681]

Other sulfonamides. Of 11 patients with meningococcic meningitis who received proseptasine, soluseptasine or both, nine recovered.[414, 1040] Six cases of meningococcic meningitis (Hobson and McQuaide) and one of meningococcal septicemia presenting a picture of "acute rheumatism" (Dimson) were successfully treated with sulfapyridine.

[Many physicians now consider sulfapyridine superior to sulfanilamide in meningococcal infections.—Ed.]

Fever therapy. A case of meningococcal septicemia hypersensitive to serum was cured by fever therapy (Rosenbluth and Stetten).

Suppurative (Purulent, Septic) Arthritis

A case of septic arthritis affecting the knee of a child with femoral osteomyelitis was reported (Cutler). *Staphylococcus aureus* was recovered. Orthodox treatment was briefly reviewed.

Articular Disease Due to Hemolytic Streptococci

Formerly a fairly large proportion of cases of septic arthritis was due to hemolytic streptococci, but since the advent of sulfanilamide this type of septic arthritis already seems to be disappearing. Only one instance of this complication was noted among many current reports of conditions due to these bacteria. In a case of hemolytic streptococcal infection reported by Butler [147] acute arthritis of a knee developed; perfect function was obtained after the use of prontosil and aspiration. This illustrates again the supreme importance of making bacteriologic diagnoses as often and as early as possible in all cases of septic arthritis and of course in all cases of septicemia or localized sepsis.[652, 739] Bliss, Long and Feinstone described clearly the criteria for the recognition of the main streptococcal groups. Physicians who are confused by current bacterial terminology will find their paper especially useful.

Sulfanilamide. Further studies on the mode of action of the drug on beta hemolytic streptococci were reported.[479, 541, 591, 606] The drug proved

very potent in saving animals with experimental hemolytic streptococcal meningitis.[12, 544] Even when local lesions were not fully controlled, the drug seemed to prevent bacterial invasion of the blood stream. [Hence the diminution of articular complications.—Ed.] Striking results were noted in the treatment of patients with various hemolytic streptococcic infections, including many cases of meningitis, the mortality rate of which has been reduced from about 92 to 97 per cent to about 14 per cent (McGinty). These references concern the excellent results in erysipelas, mastoiditis, otitis, and hemolytic streptococcal pneumonia but especially meningitis, all of which diseases formerly were frequently the cause of complicating arthritis.[30, 33, 116, 147, 150, 174, 192, 293, 366, 391, 400, 461, 515, 575, 627, 677, 845, 913, 942]

A case of *anaerobic* beta hemolytic streptococcal meningitis was also successfully treated with sulfanilamide.[882]

Neoprontosil (prontosil soluble) was used orally to treat successfully cases of hemolytic streptococcal sore throat, nasopharyngeal carriers, and two cases of septicemia intolerant to sulfanilamide (Herrell and Brown).

Arthritis of Scarlet Fever: Postscarlatinal Rheumatism

Opinions are still in conflict as to the value of sulfanilamide in scarlet fever. Hogarth concluded that it had no effect on fever, toxemia or incidence of complications. Acute scarlatinal rheumatism affected two of 115 patients given no special therapy, none of 126 patients given serum, and one of 114 patients given serum and sulfanilamide (generally small doses of the latter). In the three groups the total complications numbered 31, 29 and 25 respectively. Sako, Dwan and Platou, using larger doses of sulfanilamide, noted definitely beneficial results. Complications affected 41 (two with "arthritis") among 100 patients with scarlet fever not given sulfanilamide, but only eight (no arthritis) among a similar number given the drug. However, the duration of toxemia was not shortened thereby, hence combined serum and drug therapy was recommended. The latter also had a prophylactic value which antitoxin alone did not. Maxcy's report on changing concepts of scarlet fever is of interest.

Arthritis with Chronic Ulcerative Colitis

Subacute or chronic arthritis complicates about 4 per cent of cases of this disease. For reasons previously[3] given some physicians have concluded it represents a special entity, not merely a variety of ordinary atrophic arthritis. A woman in her fifth year of chronic ulcerative colitis first had "recurrent bouts of pain and swelling in practically all the joints of her extremities." Temporarily improved by conservative measures the disease progressed slowly until nine years later pelvic abscess and partial intestinal obstruction developed. After colectomy the intestinal and articular symptoms subsided (Campbell).

[Two years later abdominal symptoms were still absent but she experienced an acute attack of arthritis which subsided shortly after the use of irrigations to the remaining segment of the colon.—Ed.]

Preliminary experiences suggested that neoprontosil (prontosil soluble) given orally has a beneficial effect on this disease.[49, 125, 437] Others [624] found the oral use of prontosil soluble less effective at least in dogs, than its subcutaneous use. It was absorbed poorly from the intestines, and concentrations in blood were relatively low.

Rarer Forms of Specific Infectious Arthritis

1. The articular complications of the different dysenteries (bacillary, amebic) were considered by Benjafield and Halley, who reported the case of a girl with nonsuppurative destructive arthritis of a hip. Various bacteria isolated from the throat were considered insignificant, but pure cultures of an organism of the "*Flexner dysenteric type akin to Bacillus alkalescens*" were repeatedly recovered from feces despite the absence of dysenteric symptoms. The patient whose arthritis had been treated unsuccessfully for 10 months by immobilization, "recovered rapidly" when intestinal antiseptics, colon irrigation and vaccine were used.

2. Bishop reported the case of a child with burns on a foot infected with *Bacillus pyocyaneus*. The ankle was drained and apparently healed, but 15 months later the acute pyarthrosis recurred. From the incised ankle pure cultures of the bacillus were recovered. Only one similar articular infection (Pinelli, 1927) has been reported.

3. *Micrococcus catarrhalis* (*Neisseria catarrhalis*) is rarely a serious pathogen. Solomon and Tuchewicz saw a woman, aged 64 years, with acute arthritis of a knee with much swelling and pain in the joint and leg, also a foul vaginal discharge, polyuria and dysuria. Gram-negative intracellular diplococci were found in the cervix and naturally thought to be gonococci. The morphologic characteristics of *Micrococcus catarrhalis* and gonococci are identical. Similar organisms were grown from the aspirated purulent synovial effusion but were proved by various tests and fermentations to be *Micrococcus catarrhalis*, not gonococci. Treatment (aspiration, immobilization, heat, later massage and exercises) resulted in "complete restoration" of articular function. Curtis (1932) reported a case of bacteremia and acute polyarthritis from this organism.

4. The day after falling out of bed an infant had fever and acute arthritis of a hip, wrist and elbow. Therein purulent effusions developed from which *Haemophilus influenzae* and *Corynebacterium xerosis* were recovered by Weaver and Sherwood. Roentgenograms of wrist and elbow remained negative; dislocation of the femoral head occurred and was corrected by incision and open reduction. Within a month complete motion of affected joints was restored. Acute purulent monarthritis of a knee in an elderly woman was noted. *Haemophilus influenzae* were recovered.

This organism can produce pus, and has been the known cause of many suppurative processes, notably meningitis. Previously reported have been 11 cases of hematogenous pyarthrosis with influenzal meningitis and 13 cases without meningitis, practically all being in infants. From one to three joints were affected in each case. Weaver and Sherwood noted that all cases with meningitis were fatal; in all others, except one, recovery occurred, generally with excellent articular function regardless of the treatment used (aspiration, incision, lavage and closure of joints; aspiration and injection of tripaflavin or Carrel-Dakin solution).

Rheumatic Fever

Several useful reviews of the subject appeared, notably a comprehensive one by Swift and McEwen on all phases of the disease and an analysis by Schlesinger of 1000 cases of rheumatic carditis. The disease appears to be notably on the decrease in London.[234]

Predisposing Factors. 1. Geography and climate. According to Mills "rheumatic infections, and their resulting disabilities are perhaps more directly and completely conditioned by climate and weather characteristics than are any other disease states." Differences in death rate from the disease in the northern and southern states of the United States are much less striking than the differences in its incidence. Two American regions of greatest mortality are the Rocky Mountains and higher plateau states to the east, and from Iowa eastward to the coast. The survival rate of the "more vigorous people of the north" seems to be notably higher. Grinnan noted the incidence of the disease among admissions to a general hospital in Norfolk, Virginia, to be 0.25 per cent (compared to 0.9 per cent in New York City). Cardiac damage seemed to be less severe; otherwise the disease in Virginia was similar to that elsewhere. Altitude seemed a more important factor than dampness in France where the disease is more frequent in the higher center and east than in the damp west plains, but marked variations were seen in the same regions.[219] Further reports indicate the widespread nature of the disease.

It is not uncommon in the tropics and is commonly seen in South Africa [267, 314] and India.[455, 614, 920-922] Among 10,937 cases which came to postmortem examination in the medical college hospitals of India, Stott found the incidence of mitral endocarditis (largely rheumatic) to be 2.2 per cent, and to be 14 per cent of the cases of circulatory diseases.[922] In King George's Hospital, Lucknow, India, the "incidence of acute rheumatic infection" was 6 per 1000 medical admissions: 42 per cent were for acute rheumatic fever, 52 per cent for acute carditis, 6 per cent for chorea.[921] In another Indian hospital the rate was 1.2 per 1000 medical admissions.[614] The disease in India resembles that elsewhere except that its age incidence seems to be extended somewhat as compared to Europe, and rashes, chorea, and nodules were rare (Hodge).

In England Poynton regarded the factor of "macro-climate" (rain, mist, fog, cloudiness, cold, damp) not as important as that of the "micro-climate" of the patient's home (cold, damp homes, overcrowding, poor sanitation and nutrition). Hill [443] stated that climate per se has little influence on the incidence of the disease. Eskimos

and Laplanders are remarkably free of it. The factors of crowded, warm rooms, and infection spread by "carriers" are more important than variations in natural climate. According to Edstrom, the incidence of rheumatic fever in Europe is influenced not so much by dry or wet climate per se as by the passage of cyclones and anticyclones affecting the vegetative nervous system. Of interest in this connection is Poulton's consideration of the effect of wet and dry climates and weather in the causation of disease.

2. Season. Although the incidence of rheumatic fever in England is influenced by damp cold, the disease is most frequent in hot, dry years: Rowlands reconciled this apparent discrepancy by noting that the disease is most frequent after or during marked changes in humidity and temperature. The high fall incidence is related to the rapid decrease in temperature and increase in humidity. Mills concluded that the seasonal incidence in such widely scattered regions as San Francisco, Peiping (China), and Cincinnati was related to the storm waves in those areas. Stott noted the seasonal incidence in India.

3. Social and hygienic factors. Although the factor of overcrowding was notable, the family income was "adequate" in 164 of Dally's 300 London cases of juvenile rheumatism. Poynton also frequently saw the disease among children who were not poor; nevertheless, the incidence was less than that among the poor. Acute rheumatism was very uncommon among 75,000 adults and juvenile inmates of 60 British mental institutions who were well housed, well fed, well clothed, led regular lives, were segregated and under constant medical supervision. Tonsillitis, however, was frequent. Their ideal "micro-climate" was probably responsible for their exemption from rheumatic fever (Poynton).

4. Family, heredity, constitution. In England a hereditary factor is present in about 40 per cent of cases (Poynton). Read, Ciocco, and Taussig noted the incidence of rheumatic symptoms (chorea, rheumatic fever, rheumatic carditis) among the relatives of 33 rheumatic and 33 nonrheumatic children. Rheumatic symptoms affected 16 per cent of the siblings, 31 per cent of the parents, 9 per cent of the uncles and aunts, and 18 per cent of the grandparents of the rheumatic children, but only 4 per cent of the siblings, 8 per cent of the parents, 4 per cent of the uncles and aunts, and 2.3 per cent of the grandparents of the nonrheumatic children. That such a familial tendency was manifest for at least three generations strongly suggested a constitutional susceptibility to the disease. This does not eliminate the possibility that exposure is also an important factor. According to Gibson,[356] rheumatic fever does not behave as a familial disease, although it is more prevalent in some families than others; some factors in the individual child determine his tendency to the disease. Of interest in this connection is the report of Morgan and Webster of the occurrence, within two weeks, of rheumatic fever and mitral endocarditis in each of identical twins, and that of Holsti and Huuskonen on the frequent appearance of atrophic and hypertrophic arthritis and rheumatic fever among four generations of one family.

A common belief in England, recently contested (Brownlee, 1927) is that the disease develops more often among blonde and blue-eyed children than among brunette, dark-eyed children. Among Dally's 300 cases, the eyes were gray in 121, brown in 91, hazel in 53, blue in 35; hair was medium-colored in 115, dark in 96, fair in 80, and red in 9. Lack of controls makes such data of little significance, according to Findlay. Rheumatic children have a characteristic constitution, according to Dally, featured by "a decreased alkaline reserve in blood, and in urine, a deviation of the acid base balance in the direction of increased acidity."

[No proof for this idea was given.—Ed.]

In contrast to this view was that of Findlay [308] who stated that the "prerheumatic child" cannot be definitely diagnosed; indeed, his existence seems unlikely: "the term should be allowed to lapse. . . . There is nothing in the make-up of the body, either physical or chemical, which enables us to foretell the possible development of [rheumatic fever]. One must never forget the common environmental conditions of the various members of an individual family as a possible factor in this event." Contrary to the belief of others, according to Findlay, chorea does not particularly affect clever, high-strung children, and nervousness, enuresis, and digestive disturbances are not frequent precursors of rheumatic fever.

5. Sex. Of Dally's patients, 117 were boys, 183 girls. Most cases in India are in men, but this is of no significance, as Indian women receive much less medical care than men (Stott).

6. Age. In current reports the usual age incidences were reported. Eigen reported the fatal case of an infant 32 months old: a study of the rheumatic pneumonitis and myocarditis present suggested that the disease began when the infant was between 18 and 24 months old. "It is probable that first attacks of rheumatic fever frequently occur at a much earlier age than has been suspected."

General Symptomatology. The symptomatology of the disease in children (juvenile rheumatism) and in adults was again described.[34, 308-310, 356, 581, 1001, 1042] According to Findlay in juvenile rheumatism only four [common] manifestations are unquestionably due to the rheumatic toxin: arthritis, chorea, carditis, and subcutaneous nodules. None of them alone is pathognomonic of the disease, but when two or more of them are seen in combination or in sequence, then "the clinical picture is one of the most characteristic in the whole domain of pathology." Contrary to the view of many Findlay strongly opposed the view that rheumatic fever ever produces meningeal, pleural, pulmonary, or peritoneal infections. He considered erythema circinatum a rare but true rheumatic manifestation, but not erythema nodosum.

The relative frequency of the various symptoms of the disease as reported in new series [34, 234, 581, 1001] was about as stated in previous Reviews: polyarthritis and carditis respectively affected 135 and 122 of Archer's 150 patients, whose average age was 18 years. [In several large American series of cases the average age of onset of the disease was between six and ten years.—Ed.] Articular symptoms were much more frequent among Dally's juvenile pa-

tients than among those of Litchfield. Chorea affected 9 per cent of Archer's patients; it was an early symptom in 1 per cent of Dally's cases. In juvenile rheumatism the clinical picture is often not that of an acute febrile polyarthritis with carditis, but that of a low-grade chronic infectious process producing fatigue, muscle and joint pains, swollen lymph nodes, frequent colds, nose bleeds, and so forth, often with few or no laboratory abnormalities (Wolffe and Digilio).

Contrary to older views, most "growing pains" of children are now considered not rheumatic, but due to various juvenile orthopedic lesions or to the fatigue from hard playing.

Dally distinguished three types of juvenile "growing pains": (1) the largest group in which nonrheumatic pains often were associated with fatigue, irritability, and anemia, or due to postural or minor orthopedic defects (flat foot, knock knee, scoliosis) and to debility after severe illness or to psychologic maladjustment; (2) muscular or tendinous pains due to chronic rheumatism, not to chronic rheumatic fever (sedimentation rates normal or essentially so); (3) pains, which are generally articular, due to true subacute or acute rheumatic fever; several joints in succession may become painful and swollen, and there is usually some fever and an altered sedimentation rate. Nonrheumatic pains are more likely to be muscular, are generally short-lived, but frequently recur over a fairly long period of time. Rheumatic pains are more likely to be articular, less recurrent, more persistent, and often severe enough to confine the patient to bed for a couple of days. If carditis is to appear, it does so fairly soon; one is not left in doubt long (Findlay).

Excess fever (rectal 109° F.) was the unusual complication which affected a 40 year old patient of Boone: at necropsy rheumatic valvulitis, cerebral engorgement, thrombi, edema and a small pituitary hemorrhage were found.

General Considerations on the Pathology of Rheumatic Fever

The general pathologic changes of the disease were described by Collins [202] as occurring in three phases. The pathologic reactions of phase 1 occur at the height of activity of the rheumatic process, are nonspecific (diffuse or petechial hemorrhages into serous membranes, skin, bowel, or lungs; increased capillary fragility; regions of focal necrosis in parenchymatous organs) and are merely evidences of an intense toxemia. In phase 2 specific rheumatic reactions occur: granulomatous lesions which form in connective tissue and later undergo fibrosis develop within a week or so of the rheumatic attack, and are much more frequent than the acute nonspecific reactions. In this phase, four different processes regularly participate in varying degree: exudation, proliferation of mesenchymal tissues, degeneration of connective tissue, and infiltration of leukocytes. Details of these processes were described. Reactions in phase 3 are nonspecific and include changes in organs resulting from chronic carditis.

Special Clinicopathologic Data in Rheumatic Fever

1. Cardiovascular System. Of Findlay's 559 cases of acquired carditis, at least 96 per cent were rheumatic in origin. During 1936 in Philadelphia 357 deaths were reported as certainly due to, and 195 other deaths, as probably due to, rheumatic carditis. The mortality rate from rheumatic carditis was 17.6 per 100,000 population, excluding the 195 probable cases, or about 25 to 30 per 100,000 population including them (Hedley).[429] Among persons under 20 years of age, rheumatic carditis caused more deaths than pulmonary tuberculosis, and more deaths than whooping cough, measles, meningococcal meningitis, diphtheria, scarlet fever and anterior poliomyelitis combined. In Hedley's series, the mean age at death in all cases of rheumatic fever was 36.5 years.

To improve the national statistics on this disease, the United States Bureau of Census has made certain changes in the method of tabulating cardiac deaths.[258]

The incidence of rheumatic carditis among 104,163 students at 86 American colleges and universities was reported to be 11.6 per 1000 (9.5 per 1000 men, 14.9 per 1000 women). Hedley[428] reported the statistics from individual coöperating institutions. The reported incidence was largest in the smaller schools, smallest in the larger schools with well organized health services and frequent examinations of students. In the latter colleges many tentative diagnoses of carditis were discarded after the use of specialized studies not available in the smaller colleges. In other words, the reporting of a true incidence depends not so much on case-finding as on the detection and proper interpretation of murmurs and other physical signs.

According to Findlay,[310] if a murmur is located, or has its seat of maximal intensity, at the base, it is probably functional, but if the murmur has its seat of maximal intensity at the apex and particularly if it is propagated to the left, it is probably organic. Schlesinger[833] discussed the significance of systolic and diastolic murmurs in juvenile rheumatism at some length and stated that both mitral and aortic diastolic murmurs eventually disappear in some patients. McKee agreed with this conclusion as a result of his stethographic studies on 130 rheumatic children and 105 normal controls. Stethograms (Lockhart method) provide graphic evidence of the exact timing, intensity and vibration rate of murmurs.

Statistical studies were presented concerning the relative incidence and types of rheumatic valvulitis in England[787, 833] and in India.[614, 921] An extensive correlation of the electrocardiographic and pathologic findings in 113 fatal cases of rheumatic mitral disease was made by Berliner and Master. Calcareous aortic stenosis occurred much more frequently than is generally supposed; until recently its etiology was obscure. The data of Clawson, Noble and Lufkin, and of Willius and Dry, who studied 200 and 228 cases respectively, indicate that it is unquestionably a rheumatic lesion. Its symptoms and signs were described in detail. Complete heart block rarely occurs in acute rheumatic fever. Wedd described a case: during one period of syncope death seemed imminent. The patient failed to respond to epinephrine, but recovered regular ventricular rhythm after an intramuscular injection of 2 mg. of atropine.

Among 500 children with rheumatic fever or chorea, Taussig and Hecht noted 49 with definite hypertension (diastolic over 90, systolic generally over 130). In 12 cases hypertension was transient and blood pressures fluctuated widely; in 37 cases the elevated blood pressure occurred with the acute rheumatic episodes. None of the patients had nephritis. Among Dally's 300 juvenile patients, arterial pressures were generally normal.

2. Joints. Collins published new photomicrographs of the characteristic changes in joints. The paucity of cellular proliferation and the manner in which synovial tissues "always completely recover" differentiate this lesion from that of atrophic arthritis.

3. Nodules. Subcutaneous nodules appear on children more frequently than on adults: 14 per cent of Keil's [521] 181, and 10 per cent of Anderson's [29] 111 juvenile patients had them but only 4 per cent of Archer's 150 patients, some of whom were adults. The nodules may appear overnight; they are firm, seldom tender, and last from a few days to several months, then gradually disappear. Although they appear in crops, each nodule may last quite a while. Schlesinger noted their persistence for as long as three to five years. When they have apparently "disappeared," they may still persist microscopically. Earlier descriptions spoke of them as varying from the "size of a millet seed" to "that of a Barcelona nut," but their average size was "that of a split-pea" (Barlow and Warner, 1881). Some are "almost impalpable," being essentially microscopic only, hence they must be felt for as well as looked for. They were described currently as the "size of large peas to small granules" [1001] or "pinhead to large marble." [29]

Concerning their prognostic significance, Cheadle (1889) wrote: "The eruption of large nodules is almost equivalent to a sentence of death." This view is still generally held. Of Anderson's 11 juvenile patients with nodules, 10 had carditis. "When such nodules are present, we know the heart muscle is riddled with similar nodules" (Warner). The number of nodules is a rough measure of the "dose" of rheumatic infection present.

Schlesinger noted that children with 10 or less nodules were much more likely to recover (31 recovered, 7 died) than those with more nodules (5 recovered, 12 died). The prognosis was bad if 20 to 40 nodules were present. Of 90 patients with nodules, 40 per cent died generally within three to five years. Nodules were rare in children under seven years of age or after puberty. Before the age of 14 years a child with nodules has only an even chance of survival (33 deaths, 22 recoveries), but after puberty the prognosis is much better. Schlesinger noted many exceptions to these generalizations and concluded that nodules should be regarded with some anxiety but need never be considered a fatal omen.

[In this opinion we concur.—Ed.]

Originally subcutaneous "rheumatic nodules" were regarded as pathognomonic of rheumatic fever; this idea is no longer held by some physicians. Hawthorne and Keil reviewed the controversy as to whether the nodules in rheumatic fever are distinctive or similar to those seen in atrophic arthritis and other conditions. Hawthorne concluded that no absolute distinction has been established. Findlay [310] considered them similar to those of atrophic

arthritis, and did not regard the granuloma as pathognomonic of rheumatic fever: " Like Schmorl I have convinced myself that in many instances the giant cells or the so-called Aschoff bodies are not fibroblasts in origin, but are composed of detached pieces of degenerated cardiac muscle." According to Collins, the nodules are granulomas, " built-up masses of proliferating mesenchymal cells, newly formed capillaries, and areas of fibrinoid degeneration with infiltration of lymph and plasma cells," and they are not exactly similar to those of atrophic arthritis. Using supravital staining, McEwen studied nodules from 11 cases of rheumatic fever and eight of atrophic arthritis, also two syphilitic juxta-articular nodules. On section the " rheumatic " and " arthritic nodules " were " very similar." On supravital staining, in two of the eight cases the arthritic nodules were identical to the orthodox nodules of rheumatic fever, but in six cases minor variations were noted. Both types were different from syphilitic nodules. Keil concluded that the rheumatic nodules are sufficiently different from those in atrophic arthritis to warrant their distinct separation.

4. Lungs and Pleura. In some cases of rheumatic fever, migratory areas of pulmonary consolidation suddenly appear, last a variable length of time, disappear as quickly as they come and, according to some, produce no change in the clinical picture and no variation in pulse or respiration. Physicians agree on the type of pathologic reactions found, but disagree as to whether or not they are specific for the disease. Melnick examined the lungs in six fatal cases at Cook County Hospital, Chicago. Lungs were involved in a " vascular reaction of great intensity, backed up by a cellular proliferation. In the areas of greatest intensity the endothelium of the smaller vessels is injured." The process is not simply passive congestion; it is chiefly a focal process, not one of the simple inflammatory type as there are no bacteria and no necrosis. Melnick considered the reaction a hyperergic one. Continuing his studies on " rheumatic pneumonia," Gouley reviewed its pathologic features (as given in previous Reviews) and suggested that such pulmonary lesions may be an important factor in subsequent right ventricular failure. The latter is supposed to result from mitral stenosis and increased pressure in the pulmonary circulation. Gouley concluded that sometimes the chief factor in right ventricular failure is increased pulmonary pressure from the pulmonary changes themselves, a diffuse fibrosis which originally results, not from passive congestion, but from chronic rheumatic interstitial pneumonitis.

[Before accepting this view, one must recall that pulmonary fibrosis of much severer grades than that seen in rheumatic patients may occur in other diseases without right ventricular failure.—Ed.]

5. Skin and Mucosa. Among 523 cases of rheumatic fever and carditis, Keil[520] noted 181 eruptions in 163 cases listed thus: 53 rheumatic erythematous eruptions, 53 various hemorrhagic eruptions, 36 subcutaneous nodules, 11 telangiectatic eruptions, 8 scarlatiniform, 7 urticarial, 5 of erythema nodosum, 5 sweat eruptions, 3 herpes zoster. Some of these were rheu-

matic, others were not. Keil classified the 53 cases of rheumatic erythema ("rheumatic erythema multiforme") as follows: (1) a simple papular form, "erythema papulatum rheumaticum" in 14 cases; (2) ringed forms: (*a*) erythema marginatum rheumaticum in 15 cases; this is the most characteristic rheumatic erythema and (*b*) a flat "erythema annulare rheumaticum" in 24 cases. Their differing locations and appearance were described in detail. They were all transient, generally lasted from a few hours to several days; rarely for months or even years. They all indicate the presence of active rheumatic disease.

[This is a very thorough review of the subject.—Ed.]

Erythema marginatum (multiforme or circinate) affected only 13 of Schlesinger's 1000 patients with juvenile rheumatic fever. The outcome in these cases was so good that the advent of a circinate rash, even with nodules, appears to be, if anything, a welcome sign.

[There probably are exceptions to this rule.—Ed.]

Erythema annulare rheumaticum usually appears, according to some, after rheumatic carditis has occurred, during the subsidence of rheumatic infection or between recurrent attacks, and is of little prognostic import, since its severity does not parellel that of the general disease. Abramson and Tunick disputed these views; they reported two cases in which the skin lesion appeared as an initial symptom of rapidly fatal rheumatic fever; the severity of the erythema reflected that of the general disease.

Barber introduced a general discussion by several speakers on the skin manifestations encountered not only in rheumatic fever, but in other rheumatic diseases (atrophic arthritis, gout, etc.).

6. Abdomen. Contrary to the opinion of Findlay,[310] Warner considered rheumatic fever capable of inducing characteristic abdominal symptoms, and noted three children with acute rheumatism erroneously operated on for acute appendicitis. The pain is usually present in quick succession in several different regions, e.g., left iliac fossa, the epigastrium, right iliac fossa, or left hypochondrium. Antecedent or concurrent limb pains may be absent or overlooked. Sison and Austria noted the following three cases of leukocytosis and severe abdominal pain, generally epigastric.

In one case epigastric pain and tenderness, without fever, suddenly developed; they disappeared shortly to recur the next day with fever. The pain was then continuous, at times colicky and sometimes extended to the right hypochondrium. Four days later articular pains appeared; the slight epigastric rigidity and tenderness persisted and later carditis appeared. Symptoms were relieved by administration of salicylates. Tympany and left abdominal pain and tenderness developed in another case 12 days after the onset of mild febrile polyarthritis. A month later *Streptococcus viridans* was recovered from the blood and was possibly related to bacterial endocarditis. In the third case sudden epigastric pain requiring morphine developed; there was no fever. Next day the severe pain recurred with fever, epigastric rigidity and tenderness. Mild polyarthritis and evidence of recurring rheumatic carditis were noted. Symptoms disappeared on rest and administration of salicylates.

[We agree with Warner that such cases are encountered, but consider them infrequent.—Ed.]

Speculations were entertained that the pains may have resulted from peritoneal irritation, or reflexly from involvement of pericardium, pleura or abdominal aorta.

A different type of abdominal pain was present in 10 per cent of the cases of "low grade rheumatic disease" seen by Digilio, Pescatore, and Goldberg, namely, a dull gnawing, pulling, or dragging pain anywhere in the abdomen, but especially in the left upper quadrant which occurred only on locomotion: Perhaps it arose from involved spleen or abdominal lymph nodes. No other symptoms were noted except anorexia and pallor, but joint pains and mild fever often antedated the abdominal pains. Six illustrative cases were described: blood counts and sedimentation rates were normal.

[A variety of so-called rheumatic abdominal symptoms have been noted in previous Reviews. Their position will be uncertain until a pathologic explanation for them is forthcoming.—Ed.]

7. Kidney. An elderly patient of Good and Kanee had acute febrile polyarthritis and carditis; a week later headache, nausea, vomiting, acute hypertension and nephritis, later still phlebitis and pneumonitis developed; he died of uremic poisoning.

8. Brain. A case of acute hemorrhagic encephalitis and rheumatic fever was noted by Dobbs and de Saram: after death no specific rheumatic changes in the brain were found; "only one other similar case" has been seen (Alpers, 1928).

Electrocardiograms. Electrocardiograms were made by McGee in 50 cases of active rheumatic fever; in 46 cases abnormalities were found such as changes in the P-wave, in the P–R interval, widening or slurring of the QRS complex, changes in the S–T interval and depressions or inversions of T-wave. [It was not stated how often tracings were made, what percentages of the total number of tracings were normal, and how early in the disease most of the abormalities in tracings appeared. In at least five cases the electrocardiographic alterations were detected before frank symptoms of rheumatic fever. One must not always expect to find abnormalities when single tracings are made.—Ed.] Alteration in the P–R interval is accepted as one of the most characteristic features of rheumatic carditis. Keith noted such changes in mild juvenile cases with little or no clinical signs of carditis; they often bore little relationship to the severity of the disease. P–R intervals, increased more than 0.02 second (normal for children, average 0.138 second, range 0.12 to 0.17 second), were noted in 80 per cent of 86 cases of carditis, in 81 per cent of 59 cases of chorea and carditis, in 50 per cent of 43 cases of chorea and carditis, and in 58 per cent of 12 cases of arthritis without clinical evidence of carditis. In other words, an increased conduction time is the most constant and characteristic single cardiac feature of the disease. These conduction defects have been thought due to structural changes in the auriculo-ventricular node. But because they occurred even in very mild cases in which aortic lesions and probably edema of the bundle of His were not present, Keith suggested that

they were due, not to local pathologic reactions or to "toxins" but to overstimulation of the vagus which may be an essential feature of rheumatic fever. The origin of this overactivity is obscure, but its site is probably peripheral, in the terminations of the vagus (parasympathetic nerve endings) in the heart, rather than in the medulla. One rheumatic child had a systolic murmur, lengthened conduction time, repeated abdominal pain and vomiting, sometimes diarrhea. Perhaps the abdominal pain and vomiting occasionally seen early in rheumatic fever without pericarditis are due to overstimulation of the vagal nerve supply to the gastrointestinal tract.

Blood Chemistry. Blood sugar. Rheumatic carditis is rarely encountered among diabetic patients. Steincrohn wondered whether hyperglycemia of diabetes mellitus provided a protective state for the heart in the event of rheumatic fever. If so, persons susceptible to, or with, rheumatic carditis might be expected to have low or flat blood sugar tolerance curves; i.e., a high sugar tolerance. Such appeared to be the case in a number of Steincrohn's patients (47 adults with active, chronic, and 11 children with acute, rheumatic fever). Sugar tolerance curves of 24 adults and 9 juveniles were low; indeed, the curves of the latter were practically flat (average of 9 curves: blood sugar fasting 69.5, at one-half hour 90, at one hour 86, at 2 hours, 83, at 3 hours 79 mg. per cent).

Blood cholesterol. Poindexter and Bruger frequently noted hypocholesteremia in 18 cases of rheumatic carditis: blood cholesterol was below 150 mg. in 28 per cent, over 250 mg. per cent in 5 per cent. But the total average cholesterol value in these rheumatic cases was not significantly abnormal. These values contrasted with the hypercholesteremia often present in cases of arteriosclerotic or hypertensive heart disease.

The arithmetical mean for the total plasma cholesterol was 195 mg. per cent in 33 control cases, 185 in 18 cases of rheumatic carditis, 248 in 24 cases of arteriosclerotic heart disease, and 246 in 19 cases of hypertensive heart disease with arteriosclerosis. There was no significant difference in the ratios of ester to free cholesterol in the three types of heart disease. The average ratio of cholesterol ester to free cholesterol was 1.7 in the rheumatic, 1.86 in the arteriosclerotic, and 1.77 in the hypertensive cases.

Changes in blood cholesterol in rheumatic fever were also noted by Offenkrantz. During an acute rheumatic infection or exacerbation, the blood cholesterol, especially the ester fraction, was reduced. Each patient seemed to have his own normal standard and could not be compared exactly with others.

Of 100 patients with rheumatic fever, 49 were in a quiescent stage: their mean value of total serum cholesterol (and standard deviation) was 181.9 ± 23.5 mg. per cent; the mean value of free cholesterol was 50.5 ± 7.4 mg.; the percentage of free cholesterol was 27.3 ± 2.2. The total serum cholesterol was definitely lowered, and the percentage of free cholesterol was increased (depletion being ascribed to the loss of ester fraction) in 11 cases of acute rheumatic fever without cardiac failure, and in 12 cases of fluctuating activity of disease. In nine cases of active infection with cardiac decompensation and in seven of fluctuating activity, there was a moderate

fall in the total cholesterol values, but exacerbations did not produce the usual rise in the percentage of free cholesterol, indicating a reduction in both ester and free cholesterol. Five patients died: on the day of death or 10 minutes after death, there was a severe loss of esters, but only a slight loss of free cholesterol, so that the percentage of free cholesterol rose above 30 in each instance. Among the total group of 100 patients were five with unusually high values for total cholesterol (189 to 268 mg. per cent) despite active disease. The pattern of their mental behavior seemed to set them apart from the others enough to suggest that "possibly a psychiatric-functional status is associated with a particular type of cholesterol level in the blood."

Such studies may be of importance because experimental work has suggested that lipids participate selectively in antigen-antibody reactions; concentrations of blood cholesterol may constitute a definite factor in the patient's defense mechanism, and depletion of blood cholesterol may affect antibody response.

[The blood cholesterol is generally somewhat low in most chronic infections. —Ed.]

Relationship of Rheumatic Fever to Other Diseases

1. To Subacute Bacterial Endocarditis. Holmes [464] reviewed literature comparing the clinical and pathologic features of rheumatic and subacute bacterial endocarditis. Without presenting new data, he concluded that the two conditions are closely related, if not different manifestations of the same disease.

[Most pathologists do not subscribe to this view.—Ed.]

2. To Chorea. This will be discussed in the section on chorea.

3. To Atrophic Arthritis. Data for and against the idea that rheumatic fever and atrophic arthritis may be variations of the same pathologic process were briefly and inconclusively reviewed.[371, 651, 937] These data will be discussed under "atrophic arthritis." Features shared by the two diseases are of a general nature, often shared by other infections, but specific differences are sufficient to distinguish the two diseases clearly (Meakins).

4. To Erythema Nodosum. Although erythema nodosum occasionally accompanies rheumatic fever, Keil [520] did not consider it a feature of the disease or of true rheumatic origin. Among 800 cases of juvenile erythema nodosum, Wallgren saw only one case related to rheumatic fever, a rare but true instance of "rheumatic erythema nodosum." Erythema nodosum was related not infrequently to a variety of diseases of the upper respiratory tract but to active tuberculosis more frequently ("tuberculous erythema nodosum"). No clinical or pathologic distinction was found among the various types of erythema nodosum, hence it was concluded that the disease is a nonspecific allergic cutaneous reaction to several infections, possibly also to noninfectious agents. In most cases, however, erythema nodosum in children is, according to Wallgren, related to active tuberculosis. In every case assumed to be non-tuberculous tuberculin tests and roentgenologic examination of chest should be performed to rule out tuberculosis. In two cases of

supposed rheumatic erythema nodosum, Wallgren discovered unsuspected active tuberculosis.

[The conclusions of Keil and Wallgren are at variance with those of most investigators who believe that erythema nodosum results from several causes and occurs as often with rheumatic fever as with tuberculosis. The observed incidence depends largely on the nature of the clinical material under study.—Ed.]

Differential Diagnosis. Rheumatic fever must be differentiated chiefly from gonorrheal polyarthritis, from septicemia and pyemia, occasionally from acute leukemia, acute poliomyelitis, or acute brucellosis, also from acute polyarticular gout and several types of acute specific infectious arthritis.[1001] These differentiations have been given frequently.

Course, Prognosis and End Results of Rheumatic Fever

Rae generalized pessimistically as follows: of every 100 children who have rheumatic fever only one-third escape carditis, one-third die within 10 years of the initial attack; for the rest the carditis continues into adult life, killing patients in their prime. New statistics [96, 104, 503, 833] do not appreciably soften this pessimism. Except in the very young the first attack is rarely fatal; most deaths follow relapses from which patients partially or temporarily recover, but usually with a decreased cardiac reserve. Commonest causes of recurrences among Schlesinger's cases were acute tonsillitis or pharyngitis. Other causes were diphtheria rarely, occasionally (in two cases) tonsillectomy itself (how soon thereafter the exacerbations occurred was not stated). Increased carditis or pericarditis was the aftermath of these recurrences. Studying 59 ambulatory patients with presumably "inactive" or "quiescent" disease Juster noted that in most cases the disease is not really quiescent, but is mildly or definitely active, indicating its inherently chronic, progressive nature. Used as evidences of activity were altered sedimentation rates ("the most delicate test"),[833] weight loss, increased pulse rate, fever (not as useful or as frequent a sign as others), increased physical signs, leukocytosis ("the most valuable" sign),[509] appearance of nodes or chorea, and electrocardiographic changes.

Pregnancy has often in the past been regarded as a serious provocative of cardiac decompensation in rheumatic patients, one usually to be avoided. Although she did not minimize its potential seriousness, Hansen expressed the optimistic view that pregnancy has not been proved to affect the average age of death among rheumatic patients; 95 per cent of rheumatic patients will survive pregnancy; radical obstetrical procedures are seldom necessary, and modern methods of controlling or preventing cardiac failure can be applied as successfully to these patients as to those not pregnant. Many factors must be considered before allowing rheumatic patients to undergo pregnancy, and each case must be decided individually (Niehaus).

The prognosis in cases of juvenile carditis under proper treatment is better than is commonly thought, according to Schlesinger.

Of his 1000 patients observed for 4 to 10 years, 82 per cent (817 cases) were alive and well, 6 per cent (60 cases) were ill, and 12 per cent (123 cases) had died. Of the 817 patients who were "alive and well" 245 had "normal hearts." Of those with definite rheumatic carditis, 16 per cent were dead. Of 166 patients with mitral stenosis alone over one-third were ill or dead; of those (46 cases) with mitral and aortic disease, about half were ill or dead. Heart size influenced the prognosis more than the type of valvulitis present.

With the passage of time the situation becomes worse, as shown by Jones.[503] Among 1000 juvenile patients observed by Jones for an average of 10 years, by the time of their first discharge from the hospital 672 had evidence of carditis, 328 had not and hence were classified as "potential rheumatic heart disease subjects." Of the latter group 77 per cent were subsequently still free of evident carditis. Of the 672 patients with carditis, 34 per cent had died by the time of Jones' report, the condition of 28 per cent was "unchanged," of 18 per cent was progressing, of 18 per cent improving; the condition of the rest was unknown. Of the entire 1000 patients, nearly 60 per cent were able to carry on a normal physical life 10 years after the disease began, and the number with severe disease was "indeed small." But the mortality rate of 24 per cent was "distressing."

In another excellent study from the same hospital Bland and Jones noted 306 deaths among 1500 cases of juvenile rheumatic carditis seen during the past 16 years. Causes of death in the 306 fatal cases were as follows: "rheumatic fever and congestive failure" in 205 cases, "rheumatic fever" (alone) in 24 cases, congestive failure in 21 cases; thus rheumatic fever itself was the direct or most important cause of death in a total of 250 cases (82 per cent). Death was due to bacterial endocarditis in 18 cases (6 per cent; acute in 4, subacute in 14 cases), to other causes related to the heart in 9 cases (3 per cent; sudden death in 6, cerebral embolus in 3 cases), to causes unrelated to the heart in 16 cases (5 per cent) and to unknown causes in 13 cases (4 per cent). In the 250 fatal cases of rheumatic fever, 23 per cent of the patients died the first year of the disease, 11 per cent more the second, and 13 per cent more the third year (a total of 47 per cent within three years). Fifteen per cent lived two years more (total deaths within five years, 62 per cent); 85 per cent were dead by the tenth year; 10 per cent lived from 11 to 15 years, and 3 per cent had had the disease at least 16 years before they died. For the remaining 2 per cent the duration of the disease at death was unknown. Obviously the first three to five years of the disease are the most critical. The patient's age (up to 15 years) at the onset of this disease was not a significant factor as far as subsequent longevity was concerned. The terminal picture of rheumatic fever differed notably from that of the earlier phases, and frequently resembled pneumonia, acute nephritis or uncomplicated carditis. Arthritis was not a feature of the fatal illness in any case, chorea in only two cases, nodules in 49 cases, carditis in all cases. Details of the various clinical features were given.

From such studies as these the prognosis for rheumatic patients with obvious carditis has been fairly well established. Not so well established is the outlook for patients who have had one or more rheumatic attacks but still present signs of a normal heart, or at most an apical systolic murmur. Boone and Levine studied 225 such cases of "potential rheumatic heart disease" over an average period of 9.6 years: mitral or aortic valvulitis developed subsequently in only 4.8 per cent. Thus if a patient survived one attack of rheumatic fever or chorea without obvious carditis developing, he had a 96 per cent chance of escaping valvulitis during the next five years. Of the patients surviving the attack with only an apical systolic murmur called

"mitral insufficiency," the condition of 58 per cent remained unchanged, 42 per cent subsequently had frank mitral stenosis or aortic insufficiency.

Etiology and Pathogenesis of Rheumatic Fever

Factor of Infection. Useful general discussions on the probable relationship of infection to rheumatic fever were published by Gibson,[358] Goldie, and Poynton.[770]

1. Nasopharyngeal infections. Green[385] cultured the throats of 200 patients with acute rheumatic fever and of 200 nonrheumatic controls. Antecedent throat infections had affected 78 per cent of the rheumatic, 46 per cent of the controls. Hemolytic streptococci were recovered in 58 per cent (116) of the rheumatic cases, in only 30 per cent (59) of the nonrheumatic cases. Streptococci in the rheumatic group were Lancefield Group A in 87, B in 3, C in 5, G in 5 per cent, D, E, F and H in none; in the nonrheumatic group they were Group A in 42, B in 15, C in 27, D in 2 per cent, E and F in none, G in 11 and H in 3 per cent of cases with positive cultures. Thus Group A hemolytic streptococci were recovered in 51 per cent of the total rheumatic cases, but in only 13 per cent of the total nonrheumatic cases. Such data suggest again a relationship between these bacteria and rheumatic fever.

In 1934 Long and Bliss recovered from the throats of normal and diseased humans "minute" beta hemolytic streptococci different from "ordinary" beta hemolytic streptococci. Further studies were reported.[594] From the throats of normal persons such "minute" streptococci were recovered by occasional throat cultures in 12 per cent, by repeated cultures in 23 per cent, of cases. They were found rarely in throats of persons ill with a variety of acute and chronic diseases (including scarlet fever, tonsillitis, acute upper respiratory infection) but frequently in cases of diffuse glomerular nephritis of type A (acute onset preceded by acute streptococcal infection) and in 55 per cent of 146 cases of rheumatic fever or carditis. "Ordinary" beta hemolytic streptococci were found in only 30 per cent of the 146 cases. Although both groups of hemolytic streptococci were recovered frequently from rheumatic patients, the minute variety occurred with notable preponderance in those more actively diseased.

2. Blood cultures. A review of studies from 1891 on the bacteriology of the blood in rheumatic fever was made by Leslie and Spence. By the technic used in their hospital, pathogenic organisms had never been recovered (during a period of 10 years) from the blood of normal persons, or patients without definite signs of disease, nor from rheumatic patients unless they had proved subacute bacterial endocarditis. To determine whether they had been missing significant organisms, a more elaborate method for blood cultures was devised, involving a primary culture and several subcultures. Cultures were made in 26 cases of active rheumatic fever. In all cases, primary cultures were negative (after 48 hours' incubation). In 11 of the

26 cases, all subcultures remained negative. In 14 cases, a variety of nonpathogenic organisms was found; in only one case was a pathogenic organism found. The organisms in these 15 cases were considered to be airborne contaminants, as results in controls were similar. Similar negative results were noted in four cases of chorea.

3. Skin tests. Positive skin reactions to extracts of hemolytic streptococci were noted by Goldie in 77 per cent of 80 rheumatic cases and in only 32 per cent of controls. The reaction usually became positive about the second or third week of illness except in severe cases when its appearance was delayed weeks or even months. Only 27 per cent of the rheumatic cases were skin-sensitive to *Streptococcus viridans*. Of Green's [386] 105 patients with acute and subacute rheumatic fever, 75 per cent gave positive skin reactions to a stock hemolytic streptococcal *endotoxin* as compared with 24 per cent of 105 nonrheumatic controls. The percentage of reactions to hemolytic streptococcal *exotoxin* was about equal in the rheumatic and control groups. Of 32 cases of acute rheumatism, 27, 14 and 13 respectively showed skin sensitivity to endotoxins of autogenous hemolytic streptococci, *Streptococcus viridans* and indifferent streptococci. In certain quiescent cases, rheumatic activity was induced by subcutaneous injections of hemolytic streptococcal endotoxin. Admittedly, the significance of these positive tests is not clear, but Goldie regarded them as an indication of local immunity to bacterial endotoxin, and an index of the circulating anti-endotoxin. At any rate, they seem to indicate a close connection between such bacteria and rheumatic fever.

4. Agglutination tests. Hemolytic streptococcal agglutinins have been found in high titer in the blood of patients with rheumatic fever by some (Coburn and Pauli, 1932) but not by others.[4] Of Goldie's 31 cases, in 16 (51 per cent) agglutination at a titer of 1 in 200 or over was found.

5. Precipitin tests. No new studies were reported.

6. Antifibrinolysins. No new studies were reported.

7. Antistreptolysins. In 37 of 50 rheumatic cases (but in no controls) Goldie found titers of over 200 Todd units. Considering 120 units as the upper limit of normal Koerner and Poulton found elevated values (125 to 400 units) in five cases of acute rheumatic fever.

Factor of Bacterial Allergy. Goldie interpreted the aforementioned findings as evidence that rheumatic fever (and also atrophic arthritis) results from sensitization to hemolytic streptococci. Wolffe and Digilio also accepted the idea of bacterial allergy as the cause of the disease. Gibson agreed that under Von Pirquet's broad conception of allergy (an altered capacity for reacting) "rheumatism comes into the ambit of allergy," but primarily rheumatic fever is an infectious process and to place its phenomena in the same category with those of asthma and hay fever "appears to afford no help in their explanation." Aschoff also concluded that allergic reactions occur in rheumatic fever, but "to maintain that rheumatism and allergy are equivalent is fundamentally impossible." During this infectious

disease, as in tuberculosis, allergic phases will intervene, but allergy does not play the chief part, according to Aschoff. The disease is undoubtedly caused by an undiscovered specific bacterium. "The therapy of the physician must, however, never be directed against the allergic phase, but against the true infecting bacteria. The entry of an infectious disease into an allergic phase only shows us a morphological peculiarity in the response of the tissue to the irritation of the disease. To combat the latter should ever be our task."

Virus Theory. Virus-like bodies were found in various exudates from cases of rheumatic fever by Schlesinger, Signy and Amies (1935) and by Eagles, Evans, Keith and Fisher. They seemed to be particularly significant because they were generally agglutinated by the patient's serum. These workers themselves insisted that the isolation of particles resembling elementary bodies, and even their agglutination by appropriate sera, are not proof that a virus is present or that it is the cause of the disease. Such particles must be proved to possess infectivity, and be able to produce the disease or at least some constant pathologic reaction in animals. In an attempt to prove their infectivity, inoculations thereof were given intratracheally, intravenously, into peritoneum, pericardium, muscles and joints of monkeys, hens, rats, and mice (Eagles, Evans, Keith and Fisher; Schlesinger and Signy). In some cases streptococci and streptococcal products were injected simultaneously to note whether symbiosis was present.[261] All the animal experiments gave essentially negative results. No endocarditis or pericarditis was produced. Noted were certain perivascular collections of cells in the myocardium, only superficially resembling Aschoff bodies, and certain other myocardial reactions considered to be nonspecific. Either the "elementary bodies" which were isolated are not the cause of rheumatic fever, or this disease, to which no known animal is susceptible, cannot be artificially produced by simple inoculation.

[These physicians deserve much commendation for their careful work. Investigating a "new" and intriguing idea, and having apparently obtained preliminary "successes," they nonetheless continued to appraise their own work very critically, and have only made conclusions which their work, not their hopes, would sustain. Their investigations should be continued and extended.—Ed.]

Vitamin Deficiency. Further evidence was given that a vitamin C deficiency commonly exists in rheumatic fever both during the active and quiescent stages.

Rinehart and his colleagues noted normal amounts of vitamin C (average 0.7 to 0.9; optimal levels at or above 0.9 mg. per 100 c.c. of plasma) in normal and nonrheumatic controls, low amounts (average 0.3; range 0.11 to 0.68 mg.; 97 per cent of cases below 0.5 mg.) in 30 cases of acute rheumatic fever and also in 22 inactive cases (average 0.38; range 0.10 to 1.20 mg.; 78 per cent of cases below 0.5 mg.). Sherwood also noted low concentrations (0.24 to 0.77 mg.) in five cases. Kaiser noted concentrations of vitamin C (per 100 c.c. of blood) ranging from 0.5 to 1.0 mg., in 125 normal controls, 0.57 to 0.9 in 25 acute or quiescent rheumatic cases. Values were

lower in the acute than in the quiescent cases. In some of the latter, values were normal. As rheumatic patients improved, the concentration of vitamin C in their blood improved. Nonrheumatic sick children also possessed values of vitamin C in the blood nearly as low as those of the rheumatic patients.

Keith and Hickmans performed vitamin C saturation tests on rheumatic children. They were given 500 mg. of vitamin C as a test dose; if 50 mg. were excreted within 24 hours, the patient was considered normal. The average output (24 hours) in 18 acute cases was 22 mg., that of 31 convalescent patients 12 mg. Children with acute disease excreted more than convalescent patients; the latter excreted amounts equal to those of controls of similar age. Saturation tests revealed a slight deficiency in the stores of vitamin in acute cases, as compared to convalescent cases or controls. Sodium salicylate with sodium bicarbonate, and fever reactions from typhoid vaccine produced slight increases in the excretion of vitamin C in the rheumatic cases.

The interpretation of these various data is difficult. Either most rheumatic patients are simply on a deficient diet, or the disease depletes their blood of the vitamin, or the deficiency represents an inherent or acquired metabolic fault which may be an integral factor in the cause of the disease. Rinehart and his colleagues again favored the latter idea, that vitamin C deficiency is a non-specific predisposing factor. Kaiser did not regard the deficiency as due solely to inadequate diets, but felt it impossible to say whether it preceded and disposed to the disease, or resulted from it. Keith and Hickmans and Sherwood considered the deficiency a result, not the cause, of the disease.

Conclusions on Etiology. Reviewing various theories on etiology, Poynton [770] restated reasons for his dissatisfaction with the theory of bacterial allergy and for his belief in the idea that the disease represents a bacterial infection of unknown type (probably streptococcal) which spreads generally from nasopharynx, via the blood stream (but not by mass invasion) to affect distant tissues. Gibson also reviewed current ideas and stated, "Obviously no conclusion is possible at this stage. Each theory which has been put forward conflicts to a greater or less extent with the available evidence. The problem may be restated, but not answered."

[To this conclusion we certainly agree.—Ed.]

Treatment of Rheumatic Fever

There have been no outstanding new developments in treatment.

Rest. This remains the "sheet anchor" of treatment.[857] The first consideration is to provide absolute rest in bed with the patient in the position of maximal comfort, supported by pillows as necessary.[1001] Even if no carditis is evident, the minimal period of rest in bed should be one month. No change in the application of absolute rest should be made until there have been normal pulse, temperature, sedimentation rate, and no change in cardiac size and murmurs for at least six weeks. The patient then is permitted to increase his activity gradually through 5 or 6 grades (schedules given) of increased activity (Sheldon; Warner). This may take six months or more.

Salicylates. Amounts prescribed must be adequate. Daily doses advocated were 60 to 100 grains for children,[857, 1001] 150 to 200 grains for young adults, given with equal or double amounts of sodium bicarbonate. In two or three days, when symptoms begin to lessen, the doses of salicylates should be reduced, then continued for two to three weeks. If, after a satisfactory initial response from salicylates, the temperature rises again, either the dose of salicylates was reduced too rapidly, or carditis may be developing, for fever from carditis is scarcely affected by salicylates. Only rarely is it necessary to give salicylates intramuscularly or intravenously (daily for three to four days in doses of 1 grain in 1 c.c. of water for each year of the child's age; Warner). "It cannot be too strongly urged that if [salicylates in the doses noted] do not control the joint pains and pyrexia within 48 hours, it is probable that the diagnosis must be revised."

Salicyl salicylate (salysal) was preferred to sodium salicylate by Litchfield because it is practically tasteless, less toxic and equally effective in doses half that for sodium salicylate, but it reduces fever more slowly. The annoying sweating which often accompanies salicylate therapy may be controlled by the oral administration of 5 to 10 grains of camphoric acid given one hour before the anticipated seizure of sweating.[581]

[We have never used this.—Ed.]

Sulfanilamide. Despite the supposed relationship between hemolytic streptococci and rheumatic fever, sulfanilamide seems to have no beneficial effect on the course of any of the manifestations of rheumatic fever. Swift, Moen and Hirst gave about 3 to 4 gm. of the drug daily for four or five days to eight patients with chronic recurring rheumatic fever; larger amounts could not be given, and marked toxic effects were produced (increased fever, tachycardia). No benefits were noted; indeed, the rheumatic manifestations were intensified. The formation of antistreptolysins was uninfluenced by the drug. Disappointing results were also noted by Massell and Jones, who gave the drug (about 6 to 7 grains daily per 10 pounds of body weight) to 58 patients: 16 were moderately or severely ill, 25 were convalescents, 17 had inactive disease, including seven with chorea. The course of the disease was unaffected. Toxic reactions occurred frequently, especially severe fever; hence the use of the drug is "contraindicated in the presence of active rheumatic fever." In an unstated number of cases (no details given) Sheldon and Simmons and Dunn found the drug valueless, except that two cases of "rheumatic pneumonia" became afebrile. Moore gave the drug to three patients with rheumatic fever: two recovered, one died (no details).

[Sulfanilamide may prove more useful in the prevention of rheumatic exacerbations precipitated by acute hemolytic streptococcal pharyngitis than in the treatment of acute rheumatic fever. Following the oral use of neoprontosil by Herrell and Brown, throat cultures became negative in 10 of 16 carriers of hemolytic streptococci. Of special interest are the current studies (1939) of Thomas and France and of Coburn and Moore. The latter gave 30 grains of sulfanilamide daily from November

to June inclusive to 80 rheumatic children: 79 escaped hemolytic streptococcal infection and signs of rheumatic activity. Thomas and France gave 15 to 20 grains of the drug daily from November to June inclusive to 30 rheumatic patients; 30 control rheumatic patients received no drug. Major attacks of rheumatic fever affected none of those receiving the drug and four of the controls; acute beta hemolytic streptococcal infections affected none of those given the drug and at least one of the controls. No significant drug toxicity was noted by either group of investigators.—Ed.]

Other Drugs. An opportunity to prevent the expected rheumatic flare-up would surely seem to be afforded by the interval of one to four weeks which generally exists between acute nasopharyngitis and the subsequent rheumatic exacerbation, but so far little has been accomplished in this direction. Sheldon prescribed 20 to 30 grains of acetylsalicylic acid (aspirin) daily during the sore throat and for some time afterward in an attempt to prevent or mitigate the impending rheumatic exacerbation. With similar intent, Schlesinger prescribed aspirin daily for four weeks after the nasopharyngitis and believed that by this means the number of relapses and the mortality were definitely reduced. Among 27 patients given aspirin thus, 21 recovered, 6 died; mortality was 22 per cent. Among 24 patients not so treated 13 recovered, 11 died; mortality 45 per cent.

[Similar studies of larger numbers of children might give different results. Others do not support the idea that the use of salicylates will prevent rheumatic relapses. But it may mask some symptoms, e.g., fever and joint pains. Nobody has yet noted whether the use of aspirin daily during winter months would be a more effective prophylactic than its intermittent use only after acute nasopharyngitis, or whether results from aspirin would compare with those from the use of sulfanilamide given daily throughout the winter.—Ed.]

Results from the use of aminopyrine (initial doses 30 grains daily) in 10 cases of active rheumatic fever with carditis were "extremely gratifying" to Heninger and McHardy. All symptoms, including fever, tachycardia, leukocytosis, abnormal erythrocyte sedimentation rate, and joint pains, were promptly relieved, presumably also those of active carditis.

[The follow-up time was not long enough to note the eventual effect on carditis. Aminopyrine has been known to be as effective as salicylates in controlling fever and joint pains, and smaller doses than those of salicylates can be successfully used, but previous workers at the Rockefeller Institute and elsewhere, after treating large series of cases, have discontinued its use because of the fear of agranulocytosis and because it had no effect on the course of carditis.—Ed.]

Removal of Tonsils. Allan and Baylor noted subsequent recrudescences in only 44 per cent of 108 "rheumatic patients" (36 with acute polyarthritis, 46 with chorea, 16 with polyarthritis and chorea, 10 with rheumatic carditis alone) subjected to removal of tonsils and adenoids. Carditis subsequently affected only a few of those not so affected at the time of operation; hence, removal of tonsils and adenoids was recommended. Turnley also advocated tonsillectomy for all rheumatic patients if their general condition permits. He reviewed results in 3,172 cases of "rheumatism": since the latter included many varieties of "indefinite" pains, acute rheumatism

and chronic arthritis without differentiation, his statistics are of no significance. The operation is rarely fatal; out of 65,253 tonsillectomies, death occurred only six times: from hemophilia, pneumonia, heat prostration, ether narcosis, acute edema of thymus, status lymphaticus, and never from hemorrhage directly.

Meakins deplored the "perfect passion" for tonsillectomy in rheumatic fever, and considered tonsillectomy immediately thereafter "the epitome of fanaticism." After studying 150 cases, Archer concluded that tonsillectomy did not prevent or modify initial or subsequent rheumatic attacks. A postoperative exacerbation of rheumatic fever "directly" after tonsillectomy occurred in two cases. Tonsils should be removed only if they are obviously diseased or persistently harbor hemolytic streptococci, and then only when the rheumatic process has subsided (Ash; Warner). Having studied the effect of tonsillectomy on 521 rheumatic children (425 with and 96 without their tonsils at the time of the initial rheumatic attack) Ash also concluded that, whether done before or after an initial rheumatic attack, tonsillectomy did not influence the subsequent appearance or seriousness of carditis.

Vaccines; Serums. Wolffe and Digilio noted "encouraging results" (no details given) from the use of autogenous vaccines of bacteria to which patients' skins were sensitive. A stock filtrate of hemolytic streptococci was used by Wasson in an attempt to "immunize" 34 rheumatic children against subsequent attacks. Acute exacerbations affected only 6 per cent (2) of those so treated and 29 per cent (19) of 66 untreated controls. Reviewing similar studies, Warner concluded that vaccines of hemolytic streptococci and other organisms have proved of little value, and there is no reliable evidence to countenance their intravenous use. Vaccines have generally not increased immunity as measured by antibodies or decreased hypersensitivity as shown by skin tests. In doses used they have not prevented sore throats or rheumatic relapses. According to Warner, no one has apparently used smaller doses absorbed by slower methods: he stated that it may be worth while to study the effect of small doses given subcutaneously or orally.

Intramuscular injections of antiscarlatinal serum (Eason and Carpenter 1937) in acute cases unresponsive to salicylates were cautiously approved.[857, 1002] Friedman, Klein, and Rosenblum noted no effect from intravenous injections of convalescent serum into four patients with active rheumatic fever, or of serum from actively ill patients into four convalescent patients. But when serum was drawn from 11 actively ill patients, kept 33 to 86 days, and reinjected into the same patients during convalescence, in six of seven cases symptoms and signs "suggestive of the original disease" were reproduced (slight increases in pulse rate, slight fever—never over 101° F.).

[Reactions were not striking and occurred 3 to 11 days after injections. Joint pains occurred in only two cases, joint swelling only once. Perhaps the reactions were nonspecific in type.—Ed.]

Diet and Vitamins. Despite the fact that the blood of most rheumatic patients is somewhat deficient in vitamin C,[806] no notable effects from ad-

ministration of vitamin C were reported, with the possible exception of those in Mosse's case, that of a Chinaman with acute rheumatic fever who "responded dramatically" to the use of vitamin C (contained in a daily ration of 800 to 1200 c.c. of "fresh red fruit juice"). [Details of the case are meager and confusing. One cannot determine from the dates given how long the disease antedated treatment or how long symptoms continued thereafter.—Ed.] According to Kaiser vitamin C will not prevent or cure the disease. The deficiency is probably not the cause, but the result of this infection as it is of many infections. Nevertheless, the increased need of the rheumatic patients for vitamin C should be recognized, and generous amounts of fruit juices or vitamin C supplements should be prescribed.[135, 523, 860] To rheumatic children cod liver oil (2 drams) in tomato juice (1 ounce) was given twice daily by Bacal and Struthers.

Fever Therapy. Fever therapy seemed to reduce symptoms and shorten attacks in 15 cases of acute rheumatic fever (Dunn and Simmons). Several patients, previously unrelieved by other forms of therapy, noted marked relief of symptoms after the first session of fever. In three cases recurrences occurred within two weeks to 21 months. [Several fever sessions were generally given, each at intervals of four to seven days. Hence enough time elapsed for natural remissions to have occurred. No attempt was made to evaluate such therapy in preventing or moderating carditis.—Ed.] Osborne, Blatt and Neymann gave fever therapy to seven patients with carditis and chorea and to five with carditis alone. It did not harm the heart; in the first group cardiac "improvement" was sometimes noted as evidenced by improved electrocardiograms and disappearing systolic murmurs; in the second group, only one patient really improved. Ferderber noted "improvement" (not defined) in most of his patients with rheumatic fever or rheumatic carditis given fever therapy.

[None of those who have reported beneficial effects from fever therapy for rheumatic fever and carditis have followed up the cases long enough to note whether the course of the carditis has really been affected.—Ed.]

Special Treatment for the Heart. Small doses (3 to 6 minims) of digitalis were prescribed by Warner in an attempt to slow the hearts of affected children. [This is not easy to do even with large doses. Most authorities consider digitalis of value in carditis only in the presence of cardiac failure.—Ed.] Graded plans for resumption of physical activity were outlined.[41, 341, 857, 1002]

Institutional Care and Climate. Certain physicians believe that, whenever economic status permits, rheumatic children should be taken south to avoid the cold storms of winter and spring. Choice American climates are, according to Mills, the southern parts of New Mexico, Arizona, and California. Mills recommended the migration of such patients well south, preferably near the Mexican border from El Paso west, rather than to southern Florida, or the West Indies where tropical storms and long debilitating summer heat might lessen the chance for complete quiescence of the disease. Migration should be permanent, not for the winter alone. For children of parents who cannot afford the cost, convalescent camps or farms

should be established by the government in choice southwestern spots. "The total burden on public funds would probably be no more than is required by their frequent and prolonged stays in northern hospitals at high overhead costs." In such convalescent homes, problems peculiar to the disease could be studied more carefully. To date the number of such convalescent homes in the United States is so few, and the waiting list for them so long, that months may elapse before the sick child can gain admittance. Swift contrasted the inadequate existing provisions for cardiac patients with those for the tuberculous: for the latter there are in the United States and its possessions 749 institutions with 92,786 beds, and an additional 5,000 under construction. This includes 78 federal, 399 state, county and municipal, and 71 private or semiprivate institutions.

[No figures for beds available for convalescent rheumatic patients were given, but admittedly the number is very inadequate.—Ed.]

Schemes for managing a rheumatism pavilion in Montreal (Bacal and Struthers) and a convalescent cardiac school at Caldwell, New Jersey (Kaufman) were described. Some physicians [5] consider the psychologic effect of special schools bad for rheumatic children, but as a result of his study of the emotional and social development of 21 adolescent girls with rheumatic carditis Silver strongly opposed this view. Psychic disturbances of such children arise not because of their own knowledge of their disability and the limitation it imposes, but from other causes: parental overprotectiveness, "sense of guilt," and evidences that the community considers the child handicapped. The emotional and social difficulties engendered thereby can best be eliminated by adjustments in special residential schools for rheumatic children. Unquestionably, the greatest strides in the development of special rheumatism units, convalescent hospitals, and cardiac schools have been made in England [773, 344]: synopses of these valuable schemes were outlined by Furniss, Glover, and Schlesinger. In London alone provisions have been made for the special care of 1100 convalescent rheumatic children. By such care the mortality at West Wickham was reduced to 12 per cent, as compared to that of 26 per cent in other parts of Great Britain. The provision of 1.7 convalescent beds for each 1000 elementary school children was considered necessary in London.[365]

Prophylaxis. Important points in the prophylaxis of the disease are improvement of living conditions for children (proper housing, clothing, and feeding; slum clearance, development of more playing fields), careful removal of infected foci, frequent examination of school children, and special care for rheumatic suspects. Public health nurses, teachers and mothers each play an indispensable rôle in this scheme.[92, 234]

Sydenham's Chorea

Clinical Data. The clinical features of chorea were briefly reviewed.[636] Lueth found basal metabolic rates to be normal in 42 juvenile cases of acute Sydenham's chorea, regardless of its severity. The mental changes present

in 35 cases of chorea minor were grouped by Shaskan: group 1, 10 cases of chorea and severe psychosis (two with carditis); group 2, nine cases of chorea with mild mental disturbances (behavior problems, etc.); group 3, 16 cases of chorea with gross mental changes. In the milder uncomplicated cases, there were no serious disturbances in thinking or in orientation, but behavior problems were sometimes serious. In the severe cases, the hyperkinesis or akinesis influenced thinking. Hallucinations and delusions were often present. In the more severe cases, confusion and disorientation were present. Severe mental symptoms were a grave prognostic sign and were seen in older patients. Of the 8 patients without carditis in group 1, 4 died.

Pathogenesis; Relationship to Rheumatic Fever. From the time of Bright, a close relationship has generally been thought to exist between chorea and rheumatic fever, although Osler noted such a relationship in only 21 per cent of his cases of chorea. Neither bacteriology nor pathology has solved the relationship. According to some, no structures resembling rheumatic nodules have been seen in the few cases of pure chorea which have come to necropsy (McCulloch); according to others, perivascular nodules resembling Aschoff bodies have been noted in the brains of patients dead of chorea (Schroder). "If the patient with chorea dies, he dies of rheumatism or its complications. The question still remains whether he can have chorea without rheumatism." The conclusion of current writers would seem to be that generally he cannot.[930, 979]

Among 1052 rheumatic patients studied by Sutton and Dodge, chorea was present at some time in 467, absent in 585. Emotional upsets were less frequent precipitants of chorea than recent infections, especially of the rheumatic variety. The choreic children exhibited no particular personality or body type, and had "normal" or "dull normal" intelligence quotients similar to controls. Of the 467 choreic patients, 91 (about 20 per cent) had "pure chorea" (no associated rheumatic manifestations), 133 (28 per cent) had muscle and joint pains, 243 (52 per cent) had frank rheumatic attacks. At the end of 4.8 years (mean) of observation, organic carditis was found to affect 19 per cent of those who had pure chorea, 30 per cent of those with muscle and joint pains, and 73 per cent of those who had had frank rheumatic attacks (also 72 per cent of the 585 rheumatic patients who had not had chorea). Therefore Sutton and Dodge concluded that chorea must be considered not only a manifestation, but a major manifestation, of rheumatic infection. Although chorea per se is not usually a serious disease, the child who begins his rheumatic career with chorea runs a 50 per cent chance of carditis developing, a 75 per cent chance of some noncardiac rheumatic symptoms developing.

A study by Usher led to somewhat similar conclusions. Of 105 patients with chorea, on admission 56 gave a history of "pure chorea," but 27 per cent of them were found to have carditis, generally mild; 49 gave a history of chorea and other rheumatic symptoms; in these cases of "mixed chorea" carditis, often of notable severity, had developed in 65 per cent.

To stress its relationship to rheumatic fever, McCulloch spoke of chorea minor as "encephalitis rheumatica," presumably an exudative manifestation similar to that in joints, heart and elsewhere. Schroder also speculated as to whether the true cause of chorea might not be an allergic reaction, perhaps a localized edema, in the brain itself, probably in the lenticular nuclei, resulting from selective action of a rheumatic virus.

Treatment. Contrary to the view of Sutton and Dodge, focal removal seemed less important to Usher than the control of psychic trauma: he prescribed daily 45 grains of calcium gluconate and 15 grains of aspirin generally for three to four weeks to control the chorea. Sulfanilamide given for two to four weeks by Massell and Jones had no effect in seven cases of chorea.

Fever therapy continued to be the therapeutic method of choice. It was not of benefit in Shaskan's cases of chorea with severe psychosis, but was "helpful" for patients with minor mental symptoms or with behavior problems. Schmidt treated 15 patients with artificial fever; the condition of many had been resistant to fever from typhoid vaccine: 10 were promptly cured, two "improved," two did not improve, and one patient died (no further details). Osborne and his colleagues [733, 735] again reviewed their favorable results reported previously. Choreic patients of Ferderber [300] who received only five or six fever sessions (each three hours at 105 to 106° F.) became symptom free but relapsed after four to six months; those who received 8 or 10 treatments were cured of the chorea; complicating carditis was not harmed. A follow-up study by Sutton and Dodge [929] on the condition of 99 children given fever therapy as compared to 66 treated otherwise indicated that in the former group thereafter polyarthritis developed much less frequently, carditis and recurrent chorea somewhat less frequently. The mortality of the former group was also significantly lowered.

Of 48 treated and 23 untreated patients, observed one to three years, chorea subsequently developed in 32 and 38 per cent, polyarthritis in six and 32 per cent, carditis in 13 and 26 per cent, fatal carditis in three and 13 per cent respectively. Of 51 treated and 37 untreated patients observed four to six years, chorea subsequently developed in 41 and 51 per cent, polyarthritis in six and 33 per cent, carditis in 29 and 35 per cent, and fatal carditis in 2 and 11 per cent respectively. Aortic lesions developed in only one of the 99 treated cases, in seven of the 60 untreated cases.

[If subsequent work confirms these results the modification of associated or impending carditis would appear to be a more important effect of fever therapy in cases of chorea than the shortening of the chorea itself.—Ed.]

Usher alone seemed disappointed with fever therapy: to him fever induced by typhoid vaccine or by inductothermy seemed too drastic and not certainly preventive of recurring chorea.

CASE REPORTS

ADRENAL HEMORRHAGE WITH PURPURA AND SEPTICEMIA (WATERHOUSE FRIDERICHSEN SYNDROME) WITH RECOVERY; CASE REPORT *

By T. Nelson Carey, M.D., F.A.C.P., *Baltimore, Maryland*

Adrenal hemorrhage complicating septicemia is rarely suspected during life. Almost invariably it is a postmortem discovery, but usually when found it can be correlated with the clinical picture and implicated as an important factor in causing the death of the patient. That it is probably more common than realized is indicated by the admission of three cases to the University Hospital within one year. Two of these have been reported by Sacks,[1] who in a review of the literature found only 64 cases published before 1937. The third case is described in this report; recovery of the patient prevented proof of the diagnosis by autopsy.

The reports of Waterhouse [2] in 1911 and Friderichsen [3] in 1918 have given the name of the "Waterhouse-Friderichsen syndrome" to fulminating septicemia with purpura and adrenal hemorrhage. Since Sacks' report Magnussen [4] has published one and Simpson [5] two cases.

When the descriptions are detailed all cases show a striking similarity. Aegerter [6] and Sacks [1] have called attention to this. The patient is usually a child who has become suddenly ill during the course of what is, apparently, a mild respiratory infection. Vomiting, chills and fever occur, followed by collapse within a few hours. The blood pressure, when estimated, is said to be low, though few definite figures are given. Fever is usually high or remittent, but early death has precluded more than a few determinations in each case. Cyanosis is common, and with the accelerated respiratory rate, this feature may lead to a diagnosis of pneumonia. Within 12 hours after onset a petechial rash is observed on the skin; the lesions increase in size and number, and in a few hours ecchymoses 10 to 30 mm. in diameter, or even larger, may be present. The leukocyte count is usually high. Even in those cases caused by meningococcic septicemia, typical physical signs of meningitis are usually not seen, but resistance to passive movement of the extremities, headache and weakness are common, and in Aegerter's review convulsions were noted in 12 of 57 cases. Death occurs usually within 24 hours after onset.

The illness is so fulminating and death so early that complete studies are usually not done, and only after autopsy are the symptoms correlated with the characteristic pathology. Aegerter suggested studies of sodium metabolism and recommended treatment with large doses of cortical adrenal extract, sodium chloride and epinephrine. There are in the literature no reports of serum sodium

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and potassium determinations, and no reports of treatment of the syndrome by these measures.

Of the 57 cases reviewed by Aegerter 55 were examined post mortem. Bilateral adrenal hemorrhage was found in 52 and unilateral hemorrhage in three autopsies. Sacks' and Simpson's cases had bilateral hemorrhage. The glands may be completely disorganized by gross bleeding or multiple minute areas of hemorrhage may be found. Microscopic examination shows hemorrhage of variable extent, often with complete disruption and extensive necrosis of the gland.

When bacteriologic study is done the meningococcus is usually discovered to be the infecting organism, but in other instances the pneumococcus, hemolytic streptococcus and staphylococcus have been recovered by blood culture.

Case Report

The patient, F.R., was a white woman, aged 27, married, whose health had been generally good until the onset of her illness. On February 2, 1937, she contracted an acute cold with cough and profuse nasal discharge, but was well enough to continue her usual duties. During the afternoon of February 8 she had several chills and vomited. About 10:00 p.m. she felt weak and somewhat short of breath. Her physician was called and though he advised hospitalization it was refused. During the night she was restless and did not sleep. At 8:00 a.m. on February 9, pneumonia was suspected by her physician and at 9:30 a.m. she was admitted to the University Hospital where she remained until 1 p.m. February 10, 1937.

On admission to the University Hospital her temperature was 103.6° F. (rectal), pulse 120, respiration 12. Examination revealed a young woman, semicomatose, but easily aroused to a moderate degree of consciousness. The lips, ears and finger-tips were cyanotic. Respiration was shallow. Scattered over the body, especially on the forearms and antecubital fossae, were many small petechiae from 0.5 to 2.0 mm. in diameter. The pupils were small and active; the fundi could not be seen through the undilated pupils. The eardrums, mouth and throat were negative. The lungs were apparently normal, though examination was not entirely satisfactory. The heart was normal in size and position, with clear, distant, rapid and regular sounds. The blood pressure was 65 systolic and 35 diastolic. The abdomen was soft. No tenderness could be elicited on deep pressure in the costovertebral angles or in the upper abdomen anteriorly. The extremities were negative. There was no stiffness of the neck and Kernig's sign was only suggestively positive, probably because the patient resented passive motion of her extremities. The deep reflexes were moderately hyperactive and no pathological reflexes could be elicited.

As soon as the hypotension was discovered 1 c.c. of 1:1000 epinephrine was given subcutaneously without demonstrable effect. Oxygen by nasal catheter slightly decreased the degree of cyanosis. Attempted carbon dioxide hyperventilation increased the rate and depth of respiration, lessened cyanosis, and caused a rise of blood pressure to 85 systolic and 40 diastolic. The blood pressure returned to its original level when carbon dioxide was temporarily discontinued.

Hypodermoclysis of physiological sodium chloride solution was started at 11:00 a.m., February 9, with 1 c.c. of epinephrine added to each liter. After 200 c.c. had been absorbed blood was drawn for serum sodium and potassium determination. Sodium was reported as 147.7 milliequivalents per liter and potassium as 3.04 milliequivalents, both normal values. Fifty grams of dextrose in 500 c.c. of 0.8 per cent sodium chloride were given intravenously at 12:30 p.m.

Lumbar puncture was performed at 10:30 a.m. The fluid was clear, and the pressure was not measured. The cell count was reported as 21 per cu. mm. with 99

per cent polymorphonuclears and 1 per cent lymphocytes. A trace of globulin was present. No bacteria were seen on direct examination, but culture was reported on February 10 as showing *Neisseria intracellularis*, agglutinated by antimeningococcic serum in dilution of 1:1280. Blood culture produced the same organism.

The patient did not void during her stay in the hospital. Her blood non-protein nitrogen was 39 mg. per cent, sugar 126 mg. per cent, and CO_2 was 42 volumes per cent. The leukocyte count on February 9 was 8,950, with a differential formula of polymorphonuclears 88 per cent, lymphocytes 8 per cent and monocytes 4 per cent. The erythrocyte count was 4.25 million and hemoglobin 13 grams (Sahli). On February 10 the leukocyte count had increased to 22,480.

As the clinical picture was identical with that described in those patients showing massive adrenal hemorrhage at autopsy, it was decided to treat the patient with cortical adrenal extract and continue with the supportive measures noted above. Accordingly, she was given 10 c.c. of cortical adrenal extract (Parke Davis & Co.) intramuscularly at 1:15 p.m. on February 9. One c.c. of epinephrine solution was given at 4:00 p.m., followed by 10 c.c. of cortical adrenal extract (Upjohn) intravenously and 10 c.c. intramuscularly at 5:00 p.m. and again at 10:00 p.m.

During the afternoon of February 9 the patient's condition was somewhat improved, with less evidence of collapse. Her blood pressure was 85 systolic and 55 diastolic at 1:00 and 2:00 p.m., falling to 64 systolic with uncertain diastolic pressure at three o'clock. After epinephrine administration it rose to 84 systolic and 60 diastolic. The temperature varied from 105° F. to 106° F. until 10:00 p.m., then ranged from 100° F. to 101.4° F. until transfer. The heart rate continued between 130 and 140. The respiratory rate increased to 30–35 after 2:00 p.m. During the afternoon restless delirium replaced the apathetic semicoma. The purpuric spots increased rapidly in size and number, and spread over the trunk and extremities. Many of the lesions were from 1 to 3 cm. in diameter, irregular and sharply defined. The skin became ecchymotic where it was traumatized by needles.

At 9:00 p.m. February 9, though cultures of blood and cerebrospinal fluid had not been reported, treatment for meningococcic septicemia was initiated. Antimeningococcic serum was given intravenously at 9:00 p.m. and intramuscularly at 2:00 a.m. February 10, and at the latter time subcutaneous administration of 2.4 gm. of sulfanilamide was started. Intravenous administration of 500 c.c. of 0.8 per cent sodium chloride was carried out between 2:00 and 2:30 a.m.

On the morning of February 10 the patient's general condition was improved and her appearance was more suggestive of epidemic meningitis. The neck was slightly stiff, but Kernig's sign was still doubtful. Cyanosis had disappeared. Occasional muscular twitching was noted, but there were no convulsions. The mental state was unchanged. Blood pressure was 104 systolic and 70 diastolic. When the bacteriologic studies were reported she was transferred at 1:00 p.m. to Sydenham Hospital, the municipal contagious disease hospital of Baltimore City.

At Sydenham Hospital lumbar puncture was done at 4:00 p.m. Thirty c.c. of cloudy cerebrospinal fluid were removed and 30 c.c. of antimeningococcic serum replaced. The cerebrospinal fluid cell count was 5200, with 89 per cent polymorphonuclear leukocytes. *Neisseria intracellularis* were found on direct examination and grown on culture.

On February 11, 30 c.c. of serum were given intrathecally, 30 c.c. intravenously, and 5.5 gm. of sulfanilamide orally. On February 12, 45 c.c., on February 13, 15 c.c., and on February 14, 20 c.c. of serum were given intrathecally. Sulfanilamide was given orally in dosage of 1.3 gm. on February 13 and 2.6 gm. on February 16. No serum was given after February 14, but sulfanilamide was continued by mouth until February 25, with an average daily dose of 4.5 gm

The cerebrospinal fluid was sterile after February 11. The patient's general condition began to improve on February 14. There was no recurrence of the shock and prostration. The temperature finally became normal on February 25, when the cerebrospinal fluid was clear, with 11 cells per cu. mm. Convalescence was complicated by a left corneal ulcer thought to be herpetic in origin. On discharge, March 7, blood pressure was 138 systolic and 80 diastolic.

Final examination was made on July 14, 1937. At that time the patient felt very well but convalescence had been slow, as recovery was not complete until late in May. Physical examination was negative except for slight scarring of the left cornea, minimal ectropion of the left lid with loss of lashes, and a soft systolic murmur at the apex of the heart transmitted a short distance toward the axilla. Blood pressure was 130 systolic and 75 diastolic while lying down and 140 systolic and 90 diastolic while sitting.

The characteristic appearance of this patient, which agreed fully with clinical descriptions of the Waterhouse-Friderichsen syndrome, probably justifies the diagnosis of adrenal hemorrhage at the onset of the meningococcic infection. Diagnosis of the syndrome cannot be certain without autopsy. Aegerter [6] suggested studies of sodium metabolism, but these studies require determination of sodium balance, evidently impossible in such an acute illness. Loeb, Atchley, Benedict and Leland [7] reported that the average reduction of blood serum sodium was as little as 2.3 milliequivalents per day after total adrenalectomy. Certainly in an illness of only 12 hours' duration one could not expect the blood sodium level to be appreciably affected. Even in Addison's disease the blood serum sodium may be within normal limits, and the abnormality of sodium metabolism only discoverable by comparison of blood level and urinary excretion during balance studies.[8]

The many therapeutic procedures employed in this case increase the difficulty of estimating the effectiveness of the attempted specific treatment with cortical adrenal extract. It is even possible, though unreported, that spontaneous recovery may occur in meningococcic septicemia with adrenal hemorrhage. However, the unexpected recovery of this patient from the severe initial collapse, possibly as the result of the treatment outlined, suggests the use of similar measures when the diagnosis of adrenal hemorrhage is suspected.

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SUPPURATIVE ARTHRITIS DUE TO A HEMOLYTIC STREPTOCOCCUS OF THE LANCEFIELD GROUP B; A CASE REPORT*

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Lancefield [1] has described a method for the differentiation of the hemolytic streptococci into groups by means of the precipitin reaction, based on the presence in this organism of a group specific carbohydrate obtainable by acid hydrolysis. She has pointed out, and the observation has been confirmed by others, that streptococci etiologically involved in practically all cases of human infection are representatives of her group A. With Hare [2] she studied a large number of cases of puerperal sepsis and demonstrated organisms of this group in 45 of 46 cases of severe infection, the other being caused by a member of group G. In seven cases of mild infection, organisms of group B were cultured from the vagina. No other instances of infection with streptococci of the latter group appear to have been reported except three fatal cases of puerperal sepsis by Fry,[3] in which the striking features were the presence of endocarditis in two, and the tendency to localized abscess formation in the other.

It is the purpose of this report to describe a case of suppurative arthritis in which a streptococcus of group B was the etiological agent.

Case Report

A 53 year old, colored, domestic worker entered the fourth medical service of the Boston City Hospital on August 14, 1938, with a complaint of pain and swelling of the left knee and hand for five days. Family history was non-contributory, as was past history except for moderate dyspnea on exertion for one year. Ten days before her admission to the hospital six teeth had been extracted. Four days later she felt very weak and chilly, and vomited. The next day pain and swelling appeared in her left knee and hand, gradually increasing in severity until the day of entry. At that time physical examination revealed a well-developed, obese, colored female who was acutely ill. The temperature was 100.5° F.; the pulse rate 100. Examination of the head and neck was negative. The chest was clear, the heart enlarged, and the blood pressure 190 systolic and 100 diastolic. No organs or masses were palpated in the abdomen, but a hard, irregular mass was felt in the uterus on pelvic examination. Over the third and fourth left metacarpo-phalangeal joints and about the left knee there was tenderness, swelling, redness, and abnormal warmth, with limited and very painful movement in the affected joints.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

Laboratory examinations revealed a normal urine; a hemoglobin of 75 per cent Sahli, 4,000,000 red blood cells, and 10,000 white blood cells, with a differential count of 72 per cent polymorphonuclears, 17 per cent lymphocytes, 10 per cent monocytes, and 1 per cent basophiles. The Hinton and gonococcal complement fixation tests were negative. Culture of the blood was sterile. The blood uric acid was 2.2 mg. per 100 milliliters. The electrocardiogram showed left ventricular preponderance.

A diagnosis of hypertensive cardiovascular disease, fibromyomata uteri, and infectious arthritis of undetermined etiology was entertained at this time. Paracentesis of the knee was performed and 25 milliliters of thin, cloudy fluid containing 38,000 cells per cubic millimeter, all of which were polymorphonuclears, were removed, and a pure culture of weakly hemolytic streptococci was grown from it.

Following the last observation she was transferred to the sixth surgical service for orthopedic management. The course of her illness during her hospital stay is illustrated in chart 1.

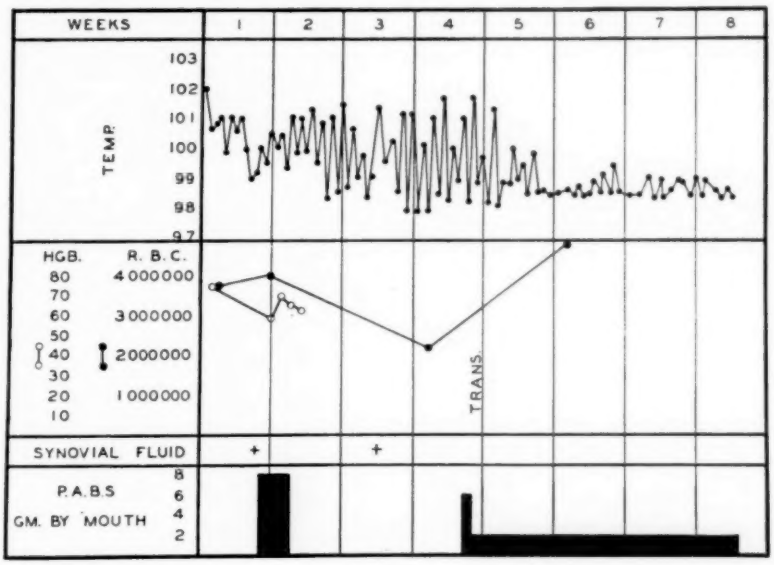

CHART I.

The temperature was of remittent type for five weeks, at which time it returned to normal by lysis. The knee was tapped again on September 6 and, when a similar streptococcus was found, sulfanilamide, in a dose of two grams daily, was begun and continued until September 27. Eight grams had been given previously on August 20 and 21. The affected limb was constantly immobilized from September 8 until the time of discharge by means of a plaster cast covering the entire leg. Anemia developing during the course of the illness necessitated a transfusion of 500 c.c. of whole blood on September 15. In other respects her course was prolonged but uneventful. The affected joints of the left hand subsided within two weeks without special therapy. At the time of discharge from the hospital she felt well and returned to her own home where immobilization of the limb in plaster for another three months was planned, eventual complete healing with ankylosis of the joint being anticipated.

BACTERIOLOGY

The majority of the strains of hemolytic streptococci of the Lancefield group B have been isolated from the mastitis of cows, from milk, and from milk

products. Certain cultural and biochemical characteristics have been described for this group. Sodium hippurate is reduced, growth occurs on 40 per cent bile agar, a final pH of 4.4 to 4.5 is reached in glucose broth, and trehalose is fermented, but not sorbitol.[1] Tillett and Garner [4] have demonstrated the failure of these organisms to produce fibrinolysin.

The biochemical, serological, and cultural characteristics of the organism, KB1J, isolated from the infected knee, as described in this report, are listed in table 1. Similar studies with K17A4 a known strain from group A, V9 a group

TABLE I

Strain	Serological Group	Reduction of Sodium Hippurate	Final pH Glucose Broth	Growth on Bile Agar		Fermentation Trehalose	Fermentation Sorbitol	Fibrinolysin
				40 per cent	10 per cent			
K17A4	A	−	4.9	−	+	+++	−	++
KB1J	B	++++	4.2	++++	++++	+++	−	−
V9	B	++++	4.6	++++	++++	+++	−	
K64	C	−	4.9	−	−			

B strain, and K64 a group C strain are included. From these observations it is possible to state definitely that this streptococcus is a member of group B. On 5 per cent blood agar surface colonies are large, flat, smooth, and gray, surrounded by a small area of partial hemolysis, quite unlike the usual small dome-shaped white colony with wide band of hemolysis that is so characteristic of the ordinary hemolytic streptococcus isolated from human sources. The other strain of this group mentioned above has a similar colonial appearance.

COMMENT

Only a few cases of serious infection in man have been reported in which streptococci of the Lancefield group B have been demonstrated to be the etiological agent. In the present case it is of interest to speculate as to the means by which an organism, ordinarily of such weak invasive qualities, reached the joints in this patient. No definite conclusions are to be drawn, but it should be noted that four days before the onset of her illness six teeth were extracted from her mouth, and it seems fair to postulate that the natural body defenses were broken down in this area, allowing a few organisms to penetrate the tissues. A transient bacteremia very likely occurred, with a focalization of bacteria in the affected joints. The relatively mild course suggests that the streptococci of this group are not as destructive as most of the members of group A.

Little specific information is available in regard to the action of sulfanilamide in infections due to group B streptococci. However, Bauer and Gunderson [5] treated four cases of bovine mastitis, a disease of cattle usually caused by organisms of this group, with this drug, and demonstrated in one instance a disappearance of the organisms from the milk during its administration and in three others a reduction of the total number of organisms. Long, Bliss and Feinstone [6] have mentioned its use in infections of the urinary tract caused by members of this group and suggest urinary levels of the drug of 250 to 300

mg. per 100 milliliters, but they have presented no other clinical data. The dosage of sulfanilamide in the case presented here was so small that it seems unlikely that it exerted more than a very slight effect on the course of the illness, but it probably exerted some inhibitory action on the growth of the organisms, and thus may have aided the natural antibody mechanism to sterilize the joint.

It is probable that practically all infections in man due to the hemolytic streptococcus are caused by members of Lancefield's group A. Since routine grouping of the strains isolated in medical and surgical practice is rarely done, no accurate statistical evidence is available. It is quite likely that, if this procedure were carried out, many more instances of infection by organisms of other groups would be discovered and the etiology of certain atypical cases clarified.

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METASTATIC CARCINOMA SIMULATING HYPERPARATHYROIDISM *

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The clinical syndrome of hyperparathyroidism has been established. The literature contains many articles by competent investigators giving the salient features of this disease with the requisites for diagnosis. Since surgical intervention, especially early in the disease, may result in cure it is important that physicians should bear this condition in mind, especially when bone pain or pathologic fracture, with roentgenologic findings of decalcification of the skeleton are present. An essential diagnostic feature of hyperparathyroidism is an elevation of blood calcium, usually to above 12 mg. per 100 c.c.

The presence of hypercalcemia even to a marked degree does not invariably mean hyperparathyroidism. Hypercalcemia can be induced by injection of para-

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thormone, or by large doses of vitamin D or of dihydrotachysterol. Also, hypercalcemia is frequently found in cases of multiple myeloma when the level of the serum protein is elevated. In 1931, Mason and Warren [1] reported a case of a woman, aged 48, with metastatic carcinoma from the breast which simulated hyperparathyroidism. The presence of a high level of blood calcium, varying between 12.9 and 17.6 mg. on 11 determinations, led to some difficulty in the diagnosis of their case. Boyd,[2] in his book on pathology, mentions two cases of metastatic carcinoma with widespread decalcification of the bone and high blood calcium determinations. One had a primary malignant lesion of the breast and the other a bronchiogenic carcinoma. Gutman, Tyson and Gutman [3] have also mentioned the association of metastatic carcinoma with high blood calcium. We wish to add a case which is almost a duplicate of that of Mason and Warren, especially in the matter of a marked elevation of blood calcium.

Case Report

A girl of 20 years was referred to the clinic with a diagnosis of suspected hyperparathyroidism. She had been in excellent health, attending college, and leading an active life up to 10 months previously, when she began to complain of severe low backache. She had lost some 12 pounds (120 to 108 pounds) during the two years before the onset of this back discomfort, but this was attributed to over-activity. The backache continued practically unchanged for five months after which she began to complain of more or less continuous pains in the legs. At that time it was thought she was suffering from rheumatic fever. Although the pains were not localized to particular joints, the severity of the discomfort and the presence of a low grade fever suggested this diagnosis. From this time on the patient was bedridden and her course was progressively downhill. Pain in the bones and joints became generalized so that motion caused great distress. Rapid weight loss of 30 pounds occurred to the time of admission. In the last six to seven weeks nausea and vomiting had been troublesome symptoms.

Physical examination revealed that the patient was thin and markedly emaciated, with a dry and shiny skin. The pulse rate was 100, the temperature normal, and the blood pressure 140 mm. of mercury systolic and 90 mm. diastolic. The muscles were markedly atrophied with loss of tone. Movement of the arms and especially of the legs produced severe pain in the lower back and shoulders. The legs were kept in a semiflexed position. No abnormalities of the bones could be found on palpation. The right breast was movable but uniformly firm and nodular. The left breast was soft and flabby. No nodes were felt. There was a scar, 10 cm. in length, over the right lower lateral chest wall from a recent rib resection.

The laboratory studies revealed that the urine contained considerable albumin and many leukocytes. The specific gravity was normal. The hemoglobin was 47 per cent (Sahli); erythrocytes numbered 2,750,000 and leukocytes, 10,350 per cubic millimeter of blood. The value for the nonprotein nitrogen was 46 mg. per 100 c.c. of blood. In the table are given the levels of the serum calcium, phosphorus and phosphatase over the course of one month. A test for Bence-Jones protein was reported as negative and the serum protein was 6.5 gm. per 100 c.c.

Roentgenologic studies of the bones, including the spine, ribs, pelvis and skull, showed a diffuse mottling type of decreased density. The ilia were more extensively involved in this process than the other bones of the skeleton, as shown in figure 1. The lung fields showed a faint, diffuse, snowflake type of mottling. Roentgenologic study of the gastrointestinal tract was reported as negative. A roentgenogram of the

FIG. 1. Extensive involvement of the ilia can be seen.

abdomen revealed a small area of increased density opposite the edge of the third lumbar vertebra in the region of the left ureter.

The case presented an interesting diagnostic problem. In favor of hyperparathyroidism was the clinical course, having as the outstanding factors bone pain, hypercalcemia, and the diffuse structural change shown by the roentgenograms of the bones.

In addition, a shadow in the region of the left ureter suggested the presence of a stone, which would favor the above diagnosis. Multiple myeloma seemed to be ruled out by the normal value for serum protein and the absence of Bence-Jones protein in the

FIG. 2. Specimen from the rib. A border of cortical bone has been partially eroded by tumor. The bone marrow and trabeculae have been replaced almost completely by fibrous marrow containing small alveoli and ill-defined epithelial cells, showing some vascularization and in places having distinct lumina in the cell masses. Rare mitoses are present (× 200).

urine. However, close scrutiny of the roentgenograms of the skeleton revealed the fact that decalcification was not the outstanding feature, but that diffuse bone destruction played the initial rôle. Beginning compression fractures in two dorsal vertebrae seemed to point to metastatic disease. Therefore, malignancy had to be ruled out before surgical exploration of the neck for a parathyroid tumor could be considered.

In the course of a careful physical examination, one of us (C. B. K.) had noted some abnormality in the right breast which had not been previously observed. To approach the problem, a portion of the breast was removed for biopsy and the specimen of the

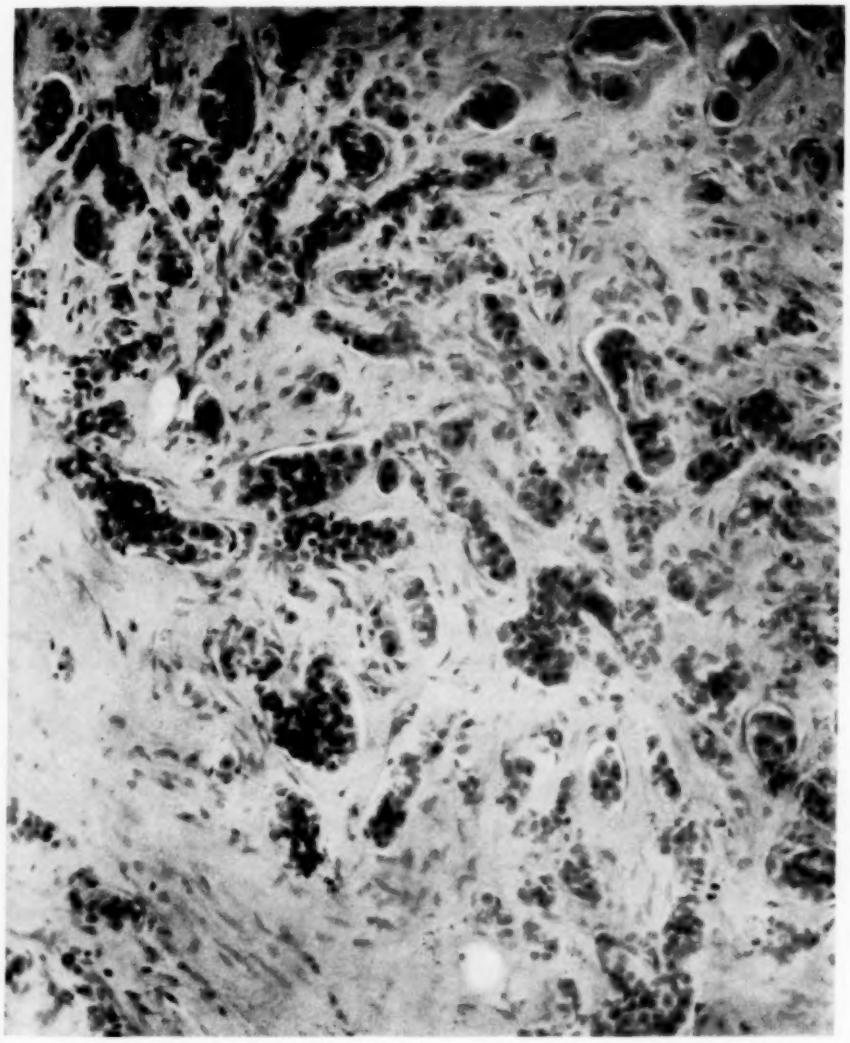

FIG. 3. The breast tissue has been completely replaced by large and small masses of compact, epithelial cells, with occasional mitotic figures. The stroma is moderately abundant. Both small blood vessels and lymphatics have been invaded by the tumor masses. There is slight variation in size of the epithelial cells. Mitoses are present but relatively few. A number of the cells contain traces of secretion (× 200).

rib which had been removed elsewhere was procured. After study of the slides,* a diagnosis was made of carcinoma simplex of the breast with metastasis to the bony skeleton (figures 2 and 3).

*We wish to acknowledge the assistance of Dr. Shields Warren for his aid in studying the slides.

Comment

This case apparently is the second to be reported in which metastatic carcinoma produced a marked elevation in the serum calcium. In the case of Mason and Warren, extensive generalized bone changes were observed, with resultant collapse of dorsal vertebral bodies similar to that observed in our case. Just as extensive changes occurred in our case in that every part of the skeleton of which roentgenograms were taken was found to be involved. Apparently the myriads of bone metastases acted through pressure or irritation to produce decalcification of adjacent bone tissue, flooding the blood stream with calcium. As a result, the level for serum calcium was substantially elevated. To produce such an increase in serum calcium there must of necessity be widespread osseous encroachment.

Ducuing [4] has recently emphasized the frequency with which carcinoma of the breast gives rise to osseous metastases. He described a type of bone pain

Table I

Serum Calcium, Phosphorus and Phosphatase

Date	Calcium, mg.	Phosphorus, mg.	Phosphatase, Bodansky units
7–19	14.9		
7–23	15.2		
8– 2	16.3		
8– 9	17.9		
8–25	15.4	3.1	4.6

associated with diffuse metastasis from the breast which had an abrupt onset in the form of "rheumatismal" crises. This is of interest since rheumatic fever was suspected early in our patient's illness. This type of symptomatic response is rare because usually the clinical picture in metastatic disease is that of localized involvement with the severest suffering associated with one region.

Conclusion

A case is reported of mammary carcinoma, which had produced generalized osseous metastasis, in a girl of 20 years. The diagnosis was at first confused with hyperparathyroidism because of a uniformly elevated value for serum calcium.

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EDITORIAL

THE INEFFICIENT TREATMENT OF ANEMIA

The studies of the past fifteen years have added greatly to our knowledge of the various types of anemia and have provided a sound basis for their intelligent and efficient treatment. As yet, however, there has not been a corresponding improvement in the methods of treatment generally employed.

Most cases of anemia can be placed in one of three large groups, depending upon the relative size and hemoglobin concentration of the red cells. The hypochromic microcytic group, with small pale cells, is associated with iron deficiency. This anemia practically always responds to the administration of adequate doses of simple inorganic iron salts. Whole liver may be of benefit as a food, particularly as a source of proteins and vitamins and, secondarily, of iron. The various liver extracts, however, have not proved to be of any practical value. The second, hyperchromic macrocytic group has cells which are larger and darker than normal. The anemia is owing to a lack of the erythrocyte maturing factor, and responds to liver, and to potent liver extracts or stomach preparations. The cases in the third group, which is quite heterogeneous, have cells which *on the average* are within normal limits as to size and hemoglobin content. The anemias of this type are due to a great variety of causes such as acute and chronic infections, chemical poisons, cancer, and various other chronic debilitating diseases. Successful treatment depends upon finding and eliminating the cause of the anemia. Neither iron nor liver preparations are of any material benefit.

Manifestly individual exceptions to this classification occur. Thus some cases of leukemia and of refractory anemias may show macrocytosis and hyperchromia and yet fail to respond to liver extract. In special cases dietary deficiencies other than a lack of iron—particularly a lack of proteins or of vitamins B and C—may cause an anemia which is resistant to treatment unless the diet is rendered adequate. Such cases are relatively uncommon, and require special treatment.

If this knowledge is to be used effectively so that the patient receives the type of treatment he requires with a minimum of unnecessary medication, a precise diagnosis must be made. At a very minimum it is necessary to determine whether the anemia is hypochromic, hyperchromic or normochromic in type. This necessitates a reasonably accurate determination of both the hemoglobin and the red cell count, procedures which are in no way difficult but do require a moderate amount of practice for accurate performance.

It is very difficult to determine directly what proportion of physicians in active practice actually utilize these methods of diagnosis and guide their treatment accordingly. A survey of the advertisements of remedies for anemia distributed to physicians by the leading pharmaceutical houses would seem to indicate that their use must be the exception rather than the rule.

The great majority of such preparations are "shot-gun" mixtures of two or more ingredients. Most of them contain iron and liver extract (erythrocyte maturing factor) in some form, or stomach concentrates. A few contain "secondary anemia liver extract"; many, vitamin supplements—brewer's yeast, B_2 complex, thiamin chloride, riboflavin, ascorbic acid. A few contain copper, and an occasional one, some other metal such as cobalt, manganese or arsenic.

More than a hundred different preparations of this type have been advertised to the medical profession within the past year or two, and if one may judge by the volume of advertising, at least 25 to 30 of them must be "large sellers." In the case of one of the most popular preparations the gross retail sales are reputed to be about three million dollars a year.

In most of these preparations the ingredients are doubtless therapeutically active and if given in a dose large enough to supply a sufficient quantity of the particular material needed they will ordinarily yield satisfactory results. The huge volume in which these preparations are now consumed, however, is less a tribute to their potency than to the clever way in which they have been advertised and promoted.

First of all, they appeal directly to those physicians who can not make blood examinations themselves and are unwilling to refer patients to others for this purpose. A circular advertising one such preparation states that it is designed for the oral treatment of all types of anemia which respond to liver therapy or the administration of iron salts. It "may be used advantageously when facilities for determining the nature of an anemia are temporarily not available or diagnosis must for other reasons be delayed."

Failure to make a precise diagnosis is particularly unfortunate in patients with anemia. In cases of anemia secondary to infection or to other organic disease, such shot-gun therapy will be futile. The underlying cause must be found and eliminated. Even in conditions such as pernicious anemia and idiopathic hypochromic anemia in which specific replacement therapy is all that is now available, a positive diagnosis is almost as essential. Without it few will persist in maintaining indefinitely a course of treatment which at best is tedious and involves an expense which is burdensome for the average patient.

In the second place, advertisers have capitalized to the utmost such statements as they can find in the literature to bolster their claim as to the advantages of such combinations. The evidence for the effectiveness of "secondary anemia liver extract" is derived almost exclusively from anima! experiments. Most of the reports of its use in man indicate that it is of little, if any, demonstrable value. Much the same is true of the effect of copper. The alleged adjuvant effect of ordinary liver extract in treating hypochromic anemia is also open to serious doubt. Statements can be found in articles by several eminent hematologists in favor of this claim and these statements have been quoted extensively by the manufacturers. Precise data to support such claims are sparse, however, and they appear to be based largely on

general impressions. Furthermore, they are at variance with the experience of the majority of observers, which indicates that in most cases of hypochromic anemia liver extract is superfluous if not entirely useless. Cases with a double deficiency do undoubtedly occur, but they are relatively rare, and merit individual attention.

There are two other practical objections to the general use of such shot-gun preparations. In many of them the amount of one of the ingredients is relatively small, and to get an effective quantity of it, a disproportionately large and correspondingly expensive dose of the preparation must be wasted. Secondly, it involves an unnecessary expense to the patient to pay for the superfluous ingredients in such a preparation, merely to save his doctor the trouble of ascertaining and indicating which one is really needed.

The addition of a trace of copper to an iron preparation need involve no appreciable additional expense. This is largely true also of the addition of ferrous sulphate or ferrous carbonate to liver extract intended for patients with pernicious anemia, although both are usually superfluous. Excessive cost becomes important, however, if unnecessary vitamin preparations are added, or if such mixtures are to be used for patients with hypochromic anemia. The ingredients which are superfluous for them account for most of the cost. Furthermore, the cases of hypochromic anemia vastly outnumber those with pernicious anemia and related types, and the total wastage is correspondingly multiplied.

The extent of this exploitation may be appreciated from a comparison of the cost of the quantity of some of these preparations which is required to provide an optimal but not excessive dose of iron. Thus, the retail cost of a daily dose of 0.8 gm. of ferrous sulphate should not exceed about four cents a day. This alone is ample for the great majority of cases of hypochromic anemia. The cost of a similar dose of iron in the form of shot-gun preparations varies greatly, but ranges from about sixteen cents to forty cents a day for a number of these most extensively used. In some cases it is much higher, reaching $1.00 to $1.50 a day in the case of some preparations containing iron in less utilizable form. Such quantities, however, are probably never actually administered. The growing use of these preparations at least has probably reduced the employment of the practically inert and extravagant parenteral injections of iron.

For those patients who need them, liver extract or vitamin supplements should be prescribed freely. An excess cost for drugs alone of from $3.60 to $10.80 a month, however, is a tax on the patient which is not justifiable when it benefits only an exceptional case. The cost of an accurate blood examination will be covered quickly by the savings it makes possible, and at the same time treatment can be established on a logical basis. This is one field in which the cost of medical care can be materially and advantageously reduced.

P. C.

REVIEWS

A Biological Approach to the Problem of Abnormal Behavior. By MILTON HARRINGTON, M.D. 459 pages; 16 × 23.5 cm. The Science Press Printing Company, Lancaster, Pa. 1938.

The author devotes the 454 pages of text to the establishment of two theses: (1) That the most useful view of behavior is purely mechanistic; and (2) that psychoanalytic theory is inadequate. Both theses are tenable and it is no doubt justifiable to attempt to prove both, except that both tasks have been executed much better elsewhere. Perhaps the author's error lies in trying to think in two directions at once. Perhaps it lies in inadequate preparation for the effort. At any rate, one finds him arguing almost entirely from analogy instead of demonstrations within the field of the material under consideration—a procedure which is of dubious propriety. He cites hypothetical cases instead of observed instances of behavior, a method which enables him to create situations to suit his needs instead of holding him to fact. In the few instances where he uses observed case material, he is much less didactic and comes much closer to an adequate statement. In dealing with the emotions, he is superficial and seems unaware of, or ignores, many of the recent advances in this field. Here he resorts to the nothing-else-but type of argument, the validity of which one must always suspect. (Page 197) "Reactions to those things that have previously occasioned pain, to which we apply the term 'fear,' are then, it would appear, due to the reactivation of the pain mechanism. In short, fear is anticipatory pain." . . . "Similarly, what we call 'hope' is in reality anticipatory pleasure." (Page 223) "This feeling of fear, it would appear, is merely pain plus the sensations arising from the bodily reaction of suspense," etc.

Moreover, while condemning the conception of conscious phenomena (desire, wish, will, etc.) as activators of behavior, he nevertheless finds it quite impossible to proceed without these terms used in this exact sense. (Page 35) "The fact of the matter is, of course, that the bulk of mankind, who cling to the doctrine of animism with such great emotional intensity, do so from motives which have little, if anything, to do with its value as a means of explaining or correlating facts. Of these motives, the strongest is, in all probability, the desire for survival." He justifies this use of terms by saying that when he uses them he really means the physiological processes underlying them. This may be true, of course, but then neither he nor anyone else knows what these processes are.

One occasionally encounters more serious contradictions within the text, of which the author seems unaware. His discussion of the "pleasure mechanism" is peculiarly confusing in this respect.

Because the author attempts to introduce new concepts, inadequately founded and of dubious utility; and since your reviewer believes that even a valid concept cannot be established by the author's method, it seems impossible to recommend this work to students as it could only lead to confusion in a field where order is just beginning to emerge.

L. F. W.

Architecture of the Kidney in Chronic Bright's Disease. By JEAN OLIVER, Professor of Pathology, Long Island College of Medicine, Pathologist, The Hoagland Laboratory. 257 pages; 20 × 29 cm.; with 112 illustrations, including 5 color and 39 aquatone plates. Paul B. Hoeber, Inc. 1939. Price, $10.00.

This book presents an amplification and extension of work begun in 1930, the progress of which appeared in the Archives of Pathology during 1933, 1934 and 1935. It represents a painstaking piece of work on which the author is to be complimented.

This investigation is based on the method of microdissection of blocks of kidney from cases of Bright's disease and recording the architectural units by camera ludica drawings and stereograms. The author has judiciously separated his objective findings from his elaborations and at the end of each chapter there is interpretative comment.

The material in this investigation consists of 23 cases previously studied from both the clinical and pathological standpoints and reported by Addis and Oliver in 1931. The majority of these cases were clinically diagnosed hemorrhagic Bright's disease (glomerulo-nephritis), but there are also included cases of the arteriosclerotic variety, degenerative pyogenic form and the amyloid kidney.

The alterations of the nephron, the transformation of the arterial system and the general alterations in kidney parenchyma are objectively worked out in each condition.

This study only emphasizes the fact that whether the process is primarily characterized by glomerular inflammation, amyloid infiltration or arteriosclerosis, each end with an organ of similar architectural pattern. One outstanding fact has been brought to light about which there has apparently been a misconception. This is that a tubule does not atrophy as a result of destruction of its glomerulus. Direct, newly formed vascular branches are demonstrated in great numbers in these contracted kidneys, connecting the afferent arteriole of the glomerulus with the intertubular capillaries.

This structural evidence, to the author's mind, compels the conclusion that there has been an excretory shift toward the tubular side, and that the circulation of blood in these contracted organs has changed from a primarily glomerular distribution to a direct tubular supply. The correlation of this rearranged function is left largely to the reader.

This book is of special interest only to those scientifically interested in the somewhat confused problem of chronic Bright's disease. It fills no particular need as far as the average physician is concerned.

C. G. W.

The Distribution of the Leukocytes in the Vascular System. By GERT VEJLENS. 239 pages. Almquist and Wiksells Boktryckeri A.-B. Upsala, 1938.

This small volume, published originally as Supplement XXXIII in 1938 in the Acta Pathologica et Microbiologica Scandinavica, is an inaugural dissertation presented by the author for the degree of doctor of medicine at the University of Upsala. The work, carried out under the direction of Professor Fahreus, represents an effort to determine the leukocyte distribution in the vascular system under varying physiological and pathological conditions. Looking upon the leukocytes as particles suspended in a flowing liquid medium, the author attempted to study the effect of alterations in the viscosity of the fluid, changes in the velocity of flow, and the influence of vessel diameter on the white cell count. Hydrodynamic principles are called upon liberally to explain many of the observed phenomena. The experiments have been carefully planned and the results evaluated statistically in many instances. The observations are summarized and an extensive bibliography is appended. Very little in the way of clinical application has been attempted and the work therefore has a limited immediate value for the general reader.

M. S. S.

The Vaginal Diaphragm; Its Fitting and Use in Contraceptive Technique. By LEMON CLARK, M.S., M.D. 106 pages. C. V. Mosby Co. 1939.

This monograph deals with only one method of contraception, i.e., the use of the vaginal diaphragm. The book contains 106 pages and 53 fine illustrations, consisting

of diagrams and pictures of wax models showing the proper fitting of the diaphragm in various normal and pathological pelvic conditions. It also contains a discussion of the various types of diaphragms and methods of fitting and inserting them, together with the indications and contra-indications for the use of these various types of methods. The book is well written and covers the subject quite comprehensively.

J. C. D.

Manual for Diabetic Patients. By W. D. SANSUM, M.D., with ALFRED E. KOEHLER, M.D., Ph.D., and RUTH BOWDEN, B.S. *227* pages; 21 × 14 cm. The Macmillan Company, New York. 1939. Price, $3.25.

This manual is written primarily for patients—"to make the patient as familiar as possible with his disorder."

Part one consists of fifteen short chapters. These chapters discuss diabetes in a style which is clear and concise. The discussion on Food Utilization proves the exception; it is too complex for the average patient to understand. The chapter on treatment with insulin is excellent and should overcome at the outset the fear and distrust with which many laymen regard this life saving medication. Adequate distribution of diet to more evenly match the action of modified insulin is advised.

Part two consists of a brief but well planned summary of practical diabetics as applied to diabetes. Forty pages are devoted to recipes. This reviewer welcomes the thirty-six recipes for desserts which are made possible by "adequate carbohydrate diets." It is obvious, however, that a dessert like pumpkin pie (C-28, P-12, F-24) would unbalance any but a high calorie diet. The book is recommended for patients, students and physicians.

L. P. G.

Hydrophthalmia or Congenital Glaucoma. By J. RINGLAND ANDERSON, M.C., M.D., B.S. (Melb.), F.R.C.S. (Edin.), F.R.A.C.S., D.O.M.S. (Lond.) *377* pages, 15.5 × 25 cm.; 116 illustrations. Cambridge University Press, London; Macmillan Co., New York. 1939. Price, *25* shillings; $7.00.

In this monograph on congenital glaucoma, Dr. Anderson takes up the question of this rather unusual condition. He bases his study on the collected findings of *205* eyes in 116 patients, as a result of a questionnaire in which he included a report on a case studied by the reviewer. The monograph is perhaps the first comprehensive resumé of the subject to appear in English, for as Sir Herbert Parsons in the Foreword points out, the last work appeared in French in 1897 by Edmund L. Gros.

The first chapter is devoted to the question of definition and etiology. In this study, Dr. Anderson shows that boys are more frequently affected than girls. The age of onset is at or very soon after birth.

In Chapter II he discusses at some length the condition of megalocornea in distinction to hydrophthalmia. The former apparently is a reversion to a primitive mammalian condition and is not, in his opinion, glaucoma.

In Chapter III he takes up the development and comparative anatomy of the involved tissues. Certainly the developmental procedure is of vast importance since many believe that the condition is always the result of developmental defects, and while the comparative anatomy may be of interest, unless the animals which are studied are known to develop congenital glaucoma, it would hardly seem to throw much light upon the subject in the human.

Chapter IV deals with the pathology of congenital glaucoma. In this chapter he reproduces many of the illustrations showing the pathology in reported cases.

In Chapter V on pathogenesis, Dr. Anderson devotes some time to the developmental theory, the inflammatory theory, and the various other theories that have been

advanced. In his summary he states that 86 per cent are apparently results of abnormal development of the mesh-work of the angle.

The treatment taken up in Chapter VI gives a review of practically all cases reported and stresses the fact that medical treatment is of practically no avail and that surgical treatment to be of value should be performed in the first year.

In Chapter VII dealing with prognosis, the author states that the outlook is very grave. However, if the cases are operated upon early, apparently about 50 per cent retain vision for at least two years. As previously stated the earlier the operative procedure, the better hope for successful outcome.

Chapter VIII under General Reflections, outlines Dr. Anderson's previous findings.

Attached to a pocket on the back binder of the book are folders with tabulations of 113 specimens examined.

This monograph is undoubtedly a masterpiece upon the subject of a very limited field in ophthalmology, and will probably remain as an authority for many years.

C. A. C.

COLLEGE NEWS NOTES

New Life Members of the College

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. Edward L. Bortz, Philadelphia, Pa.
Dr. Frederick L. Brown, New Brunswick, N. J.
Dr. Walter R. Steiner, Hartford, Conn.
Dr. Harry R. Ryan, Rutland, Vermont
Dr. Charles H. Sprague, Boise, Idaho
Dr. Lodovico Maneusi-Ungaro, Newark, N. J.

Gifts to the College Library

The following gifts to the College Library of publications by members are gratefully acknowledged:

Dr. David M. Baltzan, F.A.C.P., Saskatoon, Sask., Canada—9 reprints;
Dr. John V. Barrow, F.A.C.P., Los Angeles, Calif.—2 reprints;
Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Julius H. Comroe, Jr. (Associate), Philadelphia, Pa.—1 reprint;
Dr. O. J. Farness (Associate), Tucson, Ariz.—2 reprints;
Col. F. H. Foucar, (MC) U. S. A., F.A.C.P.—1 reprint;
Dr. J. C. Geiger, F.A.C.P., San Francisco, Calif.—1 reprint;
Dr. O. F. Hedley (Associate), Philadelphia, Pa.—13 reprints and 2 journals;
Dr. Bert F. Keltz, F.A.C.P., Oklahoma City, Okla.—2 reprints;
Dr. Kenneth R. McAlpin, F.A.C.P., New York, N. Y.—14 reprints;
Dr. M. Hill Metz (Associate), Dallas, Texas—2 reprints;
Dr. E. W. Phillips, F.A.C.P., Phoenix, Ariz.—2 reprints;
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—2 reprints;
Dr. Rafael Rodriguez-Molina, F.A.C.P., San Juan, P. R.—1 reprint;
Dr. J. K. Williams Wood (Associate), Troy, Pa.—1 reprint.

Special Board Examinations

American Board of Internal Medicine

Oral examinations of the American Board of Internal Medicine will be given just previous to the meeting of the American College of Physicians in Cleveland, April 1–5, and just in advance of the A.M.A. Meeting in New York, June 10–14. Applicants who have passed the written examination and plan to take the oral examination in 1940 should advise the secretary at least six weeks in advance of the date of the examination they desire to take. Next written examination, October 21. Applications must be filed with the secretary by September 1. Secretary, Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

American Board of Pathology

The next meeting and examination of the American Board of Pathology will be held in New York, June 10–11, 1940. Application should be filed with the Secretary, Dr. F. W. Hartman, Henry Ford Hospital, Detroit.

American Board of Pediatrics

The American Board of Pediatrics has announced the 1940 schedule of examinations as follows:

April 30 and May 1—New York, N. Y.
May 18—Kansas City, Mo.
June 1 and 2—Seattle, Wash.
November 16 and 17—Memphis, Tenn.

Application should be filed with the Secretary, Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.

American Board of Psychiatry and Neurology

The next meeting and examination of the American Board of Psychiatry and Neurology will be held in Cincinnati, May 18–19, 1940. Application should be filed with the Secretary, Dr. Walter Freeman, 1028 Connecticut Ave., N.W., Washington, D. C.

American Board of Radiology

The next meeting and examination of the American Board of Radiology will be held in New York, N. Y., June 7–10. Application should be filed with the Secretary, Dr. Byrl R. Kirklin, 102–110, Second Ave., S.W., Rochester, Minn.

Regional Meeting of Montana Members

The annual meeting of the Montana Branch of the American College of Physicians, consisting of the Fellows and Associates of the College in the state, met at Great Falls on the afternoon and evening of February 17, 1940. Thirteen of the fifteen members and three guests were present. Officers elected for the ensuing year were: Dr. F. R. Schemm, F.A.C.P., president; Dr. A. R. Foss, F.A.C.P., vice-president; and Dr. Wayne Gordon (Associate), secretary-treasurer. The afternoon program consisted of clinical papers, in some instances with the presentation of the patients, by some of the members residing in Great Falls. The evening was devoted to dinner and to a series of scientific papers. The program included: Renal Dwarfism, Dr. A. L. Gleason, F.A.C.P., Great Falls; Encephalitis, Dr. C. F. Little, F.A.C.P., Great Falls; Angioneurotic Edema, Dr. A. C. Johnson (Associate), Great Falls; Recurrent Heart Failure, Dr. F. R. Schemm, F.A.C.P., Great Falls; Recent Observations on the Principles of Radiation Therapy in Carcinoma, Dr. E. D. Hitchcock, F.A.C.P., Great Falls; Peripheral Vascular Disease, Dr. M. D. Winter, F.A.C.P., Miles City; Hypoglycemia Complicating Diabetes Mellitus, Dr. Wayne Gordon (Associate), Billings; and Pariarteritis Nodosa, Dr. F. H. Crago (by invitation), Great Falls.

On January 1, 1940, Dr. Lowell D. Snorf, F.A.C.P., was appointed Chief of the Medical Staff of the Evanston Hospital. Dr. Snorf succeeds Dr. James G. Carr, College Governor for Northern Illinois, who retired.

Dr. Louis Faugeres Bishop, Jr., F.A.C.P., addressed the Cuban Society of Cardiology on the subject of "Heart Block," Friday, February 23, 1940, in Havana, Cuba.

Lieutenant Colonel James Stevens Simmons, (MC), U. S. A., F.A.C.P., who for the past three years has been on duty as Assistant Corps Area Surgeon at Headquarters, First Corps Area, Boston, Mass., was transferred on February 15 to the Professional Services Division of the Office of The Surgeon General, U. S. Army, Washington, D. C.

Among the speakers who will address the Section on Gastro-enterology of The Medical Society of New Jersey at its 174th Annual Meeting, to be held at Atlantic City, June 4–6, 1940, will be the following:

Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, Pa.
Dr. Clarence L. Andrews, F.A.C.P., Atlantic City, N. J.
Dr. Charles L. Brown, F.A.C.P., Philadelphia, Pa.
Dr. Herbert Thomas Kelly, F.A.C.P., Philadelphia, Pa.
Dr. Manfred Kraemer, F.A.C.P., Newark, N. J.
Dr. Thomas FitzHugh, Jr., F.A.C.P., Philadelphia, Pa.
Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa.
Dr. William A. Swalm, F.A.C.P., Philadelphia, Pa.
Dr. L. M. Morrison (Associate), Philadelphia, Pa.
Dr. C. C. Beling, F.A.C.P., Newark, N. J.
Dr. David Ward Scanlan, F.A.C.P., Atlantic City, N. J.

A joint session of the Section on Medicine and the Section on Gastro-Enterology will be held Tuesday morning, June 4, 1940. Dr. Thomas M. Kain, F.A.C.P., of Camden, N. J., is chairman of the Section on Medicine; Dr. Hyman I. Goldstein (Associate), of Camden, N. J., is chairman of the Section on Gastro-Enterology.

Dr. Fred M. Smith, F.A.C.P., Iowa City, Iowa, will participate in the annual session of the Idaho State Medical Association in Sun Valley, September 11–14, 1940.

Dr. Maxwell Finland, F.A.C.P., Boston, Mass., and Dr. Josephine B. Neal, F.A.C.P., New York, N. Y., presented a symposium on the treatment of meningitis before the New England Pediatric Society, February 7, 1940.

Dr. Ernest H. Gaither, F.A.C.P., Baltimore, Md., addressed the Section on Medicine and Pediatrics of the Academy of Medicine of Northern New Jersey, January 9, 1940, on "Modern Aspects of Peptic Ulcer Therapy."

Dr. George Harlan Wells, F.A.C.P., Philadelphia, Pa., addressed the Atlantic County Medical Society of New Jersey on "Cause and Treatment of Congestive Heart Failure," January 12, 1940.

Dr. Conrad Wesselhoeft, F.A.C.P., Boston, Mass., addressed the Medical Society of the County of Albany, Albany, N. Y., January 24, 1940, on "Advances in Management of Infectious Diseases."

On January 16, 1940, Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, addressed the Academy of Medicine of Cincinnati on "Use of Liver and Iron in the Treatment of Anemia."

Among the guest speakers at the fourth annual meeting of the Rhode Island Public Health Association, held in Providence January 23, 1940, with tuberculosis control as the topic of discussion was Dr. Herbert R. Edwards, F.A.C.P., New York, N. Y. Dr. Edwards is Director of the Tuberculosis Bureau of the New York City Department of Health.

Dr. John H. Musser, F.A.C.P., Professor of Medicine, Tulane University of Louisiana School of Medicine, New Orleans, La., delivered a public lecture, sponsored by the Chicago Medical Society and the Chicago Heart Association, on "The Growing Importance of Coronary Disease," in Chicago, February 7, 1940.

Among the officers appointed by the Society of Medical History of Chicago, January 31, were the following: President—Dr. Ernest E. Irons, F.A.C.P.; Secretary-Treasurer—Dr. George H. Coleman, F.A.C.P.; Councilors—Dr. James B. Herrick, F.A.C.P., and Dr. David J. Davis, F.A.C.P.

Among those who addressed a recent meeting of the Jefferson County Medical Society of Louisville, Ky., were the following:

Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill., "Some Important Complications of Tuberculosis;"

Dr. Bayard T. Horton, F.A.C.P., Rochester, Minn., "Use of Histamine and Histaminase in Clinical Medicine."

Dr. James B. Herrick, F.A.C.P., Chicago, Ill., addressed the Cleveland Medical Library Association at its annual meeting, January 19, on "Jean-Baptiste Bouillaud and His Contributions to Heart Disease."

Dr. George E. Pfahler, F.A.C.P., Philadelphia, Pa., Professor of Radiology at the University of Pennsylvania Graduate School of Medicine, was honored at a dinner, January 25, 1940, sponsored by the Philadelphia Roentgen Ray Society. Among the speakers at this dinner was Dr. Joseph McFarland, F.A.C.P., Emeritus Professor of Pathology at the University of Pennsylvania School of Medicine.

MINUTES OF THE BOARD OF REGENTS

Philadelphia, Pa., December 17, 1939

The regular autumn meeting of the Board of Regents of the American College of Physicians was called to order at 10:20 a.m., December 17, 1939, by the President, Dr. O. H. Perry Pepper, with Mr. E. R. Loveland acting as secretary, and with the following present:

O. H. Perry Pepper, *President*
James D. Bruce, *President-Elect*
J. Morrison Hutcheson, *Third Vice-President*
William D. Stroud, *Treasurer*
George Morris Piersol, *Secretary-General*

David P. Barr
Ernest B. Bradley
Sydney R. Miller
Walter W. Palmer
Robert A. Cooke
Ernest E. Irons
D. Sclater Lewis
Hugh J. Morgan
James E. Paullin
Francis G. Blake
Reginald Fitz
Charles T. Stone
Maurice C. Pincoffs
Charles H. Cocke

Specially invited guests to this meeting included Dr. William Gerry Morgan, Historian; Dr. James Alex. Miller, Chairman of the Finance Committee and the Committee on Survey and Future Policy; and Dr. Jonathan C. Meakins, a member of the Committee on Fellowships and Awards, the Committee on Survey and Future Policy and also of the American Board of Internal Medicine.

The Secretary, Mr. E. R. Loveland, read abstracted Minutes of the preceding meeting of the Board of Regents, April 29, 1939, and also the resolutions adopted at the meetings of the Board of Regents at New Orleans in March, 1939. The abstracted Minutes were approved as read.

The Secretary read communications as follows, each acted upon individually, as indicated:

(1) Letters from Dr. Samuel A. Shelburne and Dr. M. D. Levy concerning the inclusion in the Directory of the College of additional biographical data, especially internships and residencies for each member.

On motion by Dr. Paullin, seconded by Dr. Pincoffs, and regularly carried, it was

RESOLVED, that action on the matter be deferred until the time for the preparation of the next edition of the Directory.

(2) Letter from Dr. Walter A. Bastedo concerning representation on the U. S. Pharmacopoeial Convention.

On motion by Dr. Fitz, seconded by several and regularly carried, it was

RESOLVED, that a letter be written in the name of the College, asking that the American College of Physicians be listed as supporting the Convention, and that the President be authorized to appoint delegates, their expenses to be paid by the College.

Dr. Virgil Simpson, of Louisville, and Dr. Torald Sollmann, of Cleveland, were suggested as College delegates to the Convention.

(3) Letter from Dr. Leo Kahn, Research Assistant to Senator Desmond, Albany, N. Y., concerning state examinations for specialists.

President Pepper pointed out that this would set up an additional licensing board, which possibly would be copied in other states, and that it would be at variance with the activities of the American Board of Internal Medicine.

Dr. Pincoffs stated that it was obviously in the hopes of forestalling such activity that the American Board was formed, and that the great disadvantage of having separate boards in every state is obvious.

On motion by Dr. Maurice C. Pincoffs, seconded by Dr. Hugh J. Morgan, and regularly carried, it was

RESOLVED, that the President of the College shall address a letter to Senator Desmond, Albany, N. Y., expressing the opinion that this College does not favor the formation of such boards, and pointing out the disadvantages thereof, and stating that our College has coöperated in the formation of the American Board of Internal Medicine, the purpose of which was to prevent separate and individual state licensing boards in the specialties.

The disapproval of the College was based primarily on lack of necessity, because the certifying boards already take care of this matter, and, therefore, it is not a matter of complete disagreement with the Senator from Albany.

(4) A communication received by the President as Chairman of the Executive Committee of the Board of Regents, referring to the context of presidential addresses.

Certain of the expressions of opinion in some of the recent presidential addresses had not pleased the membership.

President Pepper pointed out that it would be difficult for the Board of Regents to dictate just what the President should say, but that he felt it proper that the Board should say to each President, and that each President should know that there has been some criticism concerning controversial matters.

Continuing, President Pepper said, "Your present executive finds himself denied almost every subject for a presidential address by one or another of these letters. Everyone agrees that the address should be inspiring, touch on important matters, should not be merely a report on the state of the College, although some think that is all it should be; that it should not touch on national or medical politics, should not touch on socialized medicine, should not touch too much on ethics, should not be a scientific contribution, should not be an attempt to be humorous—which all leaves the President in an almost impossible situation, although the President is fully in sympathy with some of the criticisms that have been made."

DR. PAULLIN: "Mr. President, I think you have stated the complaints that have been voiced from the groups and from individuals who have contacted me as being a member of the Board of Regents. In various sections of the part of the country from where I come they thought that since the Presidential Address is delivered at a time when new members are inducted into the College and since they assumed the address was delivered more or less to them as new members of the College, that they should be informed more of the activities of the College, of the purposes of the College, what the College had accomplished and what it intended to do, and not a learned or scholarly talk about possible advances in medicine. In other words, they wanted to know more of the College than they did of the things that are ordinarily discussed in state medical societies and county medical societies, and the American Medical Association. They have the idea that this College represents something more than a political organization attempting to fight for certain principles in the practice of medicine. They feel that the College is a separate and distinct organization from that and represents really the cream of medical thinking and medical practice and medical ideals."

DR. HUGH MORGAN: "I would like to go on record, if you are going to close the discussion, as stating that I think for a learned society such as ours, it is a pretty curious situation for the Regents at great length to consider what the President is going to talk about. Perhaps this is an indication that we should educate some of our members to the fact that it is all right for a person to have attitudes and points of view and to air them, and if we honor a man by making him President of this society, we can certainly tolerate his attitudes and personal opinions without being contaminated or without in any sense compromising the position of the society. I just feel that way about it and I don't think it makes a bit of difference what the President talks about, if we are what we say we are."

No special action was taken by the Board of Regents regarding directions for Presidential Addresses.

(5) A letter from Dr. Cornelius O. Bailey, of Los Angeles, concerning an increase in the number of doctors and possible consolidation of the medical and dental professions.

Discussion of this communication was left for inclusion within the report of the Committee on Public Relations.

President Pepper pointed out that one of the matters of incompleted business from the Regents' meetings at New Orleans was action concerning the representation of this College on the Gorgas Memorial. He asked if any one was ready to speak on the matter. Since there was no discussion, the subject was laid on the table for further consideration at the Cleveland meeting, March 31, 1940.

The Secretary-General, Dr. George Morris Piersol, presented the following report, which was accepted as read:

"Since the last meeting of the Board of Regents, 31 Fellows and 10 Associates have died, as follows:

Fellows:

Allyn, Herman B., Philadelphia, Pa., November 6, 1939
Barksdale, George Holt, Charleston, W. Va., October 8, 1939
Bridges, Milton A., New York, N. Y., August 19, 1939
Dube, Joseph E., Montreal, Que., November 25, 1939
Edson, Philips Josiah, Pasadena, Calif., July 6, 1939
Elliott, Charles A., Chicago, Ill., June 26, 1939
Felts, Robert L., Durham, N. C., May 27, 1939
Fligman, Louis H., Helena, Mont., July 18, 1939
Franklin, George Charles Henry, Fort Leavenworth, Kan., April 23, 1939
Friedlander, Alfred, Cincinnati, Ohio, May 28, 1939
Hruby, Allan Joseph, Chicago, Ill., November 18, 1939
Jackson, Byron Hubbard, Scranton, Pa., May 16, 1939
Kamp, Joseph C., Casper, Wyo., May 13, 1939
Keeney, Bayard G., Shelbyville, Ind., October 11, 1939
Lineback, Paul Eugene, Emory University, Ga., February 28, 1939
Macgregor, John A., London, Ont., September 20, 1939
MacKenzie, Alexander John, Toronto, Ont., March 3, 1939
Norbury, Frank Parsons, Jacksonville, Ill., March 14, 1939
O'Malley, Mary, Buffalo, N. Y., January 30, 1939
Pfotzer, Roy G., Buffalo, N. Y., August 9, 1939
Rice, James Francis, Watertown, N. Y., August 3, 1939
Roberts, Carroll J., Buffalo, N. Y., April 6, 1939
Rupert, Mary P. S., Bala-Cynwyd, Pa., July 21, 1939
Rypins, Harold, Albany, N. Y., August 25, 1939

Smith, S. Calvin, Philadelphia, Pa., July 31, 1939
Soper, Willard Burr, New Haven, Conn., October 30, 1939
Stone, Charles W., Cleveland, Ohio, December 9, 1939
Stoner, Willard C., Cleveland, Ohio, November 16, 1939
Tappan, John W., El Paso, Tex., September 2, 1939
Trossbach, Herman, Bogota, N. J., October 1, 1939
Weigand, Frank J., Richmond Hill, N. Y., October 29, 1939

Associates:

Belknap, C. Herbert, Detroit, Mich., May 4, 1939
Cutler, Oran Idnire, Loma Linda, Calif., September 15, 1939
Murphy, John A., Philadelphia, Pa., June 13, 1939
O'Brien, Arthur Burke, Rochester, N. Y., July 6, 1939
Slaymaker, Samuel R., Chicago, Ill., May 3, 1939
Stein, Maurice Isaac, Harrisburg, Pa., August 15, 1939
Vrtiak, Emil George, Chicago, Ill., August 7, 1939
Walker, Thaddeus, Detroit, Mich., June 13, 1939
Walsh, John E., Washington, D. C., June 22, 1934
Yudelson, Albert B., Chicago, Ill., August 27, 1939

"Since the last meeting of the Board of Regents, the following Fellows have become LIFE MEMBERS of the College:

Edward L. Tuohy, Duluth, Minn.
Clarence L. Hyde, East Akron, Ohio
Clifford David Mercer, West Union, Iowa
Ernest John Aten, Ambridge, Pa."

The following report by the Committee on Public Relations was presented by the Chairman, Dr. James E. Paullin. The various matters recommended therein were acted upon separately and the report as a whole, upon motion by Dr. Paullin and seconded by Dr. Piersol, was approved and accepted as read:

"The following members of the Committee were present: Drs. Pepper, Cooke and Paullin.

"The substance of communications which have been referred to the Committee were sent to Drs. Walter L. Bierring, of Des Moines, and Noble Wiley Jones, of Portland, Ore., before the meeting of the Committee. Replies were received concerning all matters referred to them. Your Committee recommends to the Board of Regents the following:

"Acceptance of the resignations of Dr. Maud Loeber, New Orleans, La.; Dr. Ernst L. Schaible, Gary, Ind.; and Dr. George S. Lape, Binghamton, N. Y.

"We recommend that the following matters be filed as information:

A communication from Mr. I. H. Rubenstein, of Chicago;
A communication from Dr. William H. Walsh, Chicago;
A communication from the Service Clubs Post No. 546 of the American Legion concerning matters relating to the increase of medical students is without the jurisdiction of the American College of Physicians.
A communication from Dr. L. D. Boonshaft, of Los Angeles, concerning the regulation and standards for group practice of medicine is without the jurisdiction of the American College of Physicians.
A communication from Dr. Edward W. McCloskey, of Philadelphia, concerning the furnishing of hospital records to osteopaths, etc., is without the jurisdiction of the American College of Physicians.

A communication from Dr. Ben R. Heninger, of New Orleans, concerning the use of an electrocardiograph on private patients in hospitals where ample facilities for such are available in the hospitals, and asking for an expression of opinion from the American College of Physicians. We wish to recommend that this is a matter for local solution.

The communication from Dr. J. N. Baker, Secretary of the Medical Association of the State of Alabama, requests that medical men be memorialized by Postmaster General of the United States having stamps struck in their honor. We thought this was a very worthy thing to be done."

President Pepper suggested that the Executive Secretary take care of all required communications, with the exception of the one to Dr. J. N. Baker concerning memorializing certain medical men by having postage stamps struck in their honor, the Chairman of the Committee to state that the American College of Physicians sympathizes with the move.

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, reported that his Committee on the previous day had reviewed the credentials of 150 candidates for Fellowship and 182 candidates for Associateship, and that an analysis of the recommendations was as follows:

A. Candidates for Fellowship:

(1) Recommended for election to Fellowship, 12–16–39	
(*a*) Advancement from Associateship	104
(*b*) Election directly to Fellowship	19
(2) Recommend election of advancement to Fellowship "as of March 31, 1940"	9
TOTAL, Fellowship elections recommended	132
(3) Recommended election to Associateship first	3
(4) Deferred for further qualifications	9
(5) Rejected	6
	150

B. Candidates for Associateship:

(1) Candidates recommended for election 12–16–39	146
(2) Fellowship candidates recommended for election first to Associateship	3
TOTAL, Associateship elections recommended	149
(3) Deferred for further qualifications	20
(4) Rejected	14
(5) Withdrawn	2
	185

Chairman Miller distributed a list of all the names of candidates for review by the Board of Regents, and questions were answered concerning any and all candidates.

Upon motion by Dr. Sydney R. Miller, seconded by Dr. James E. Paullin, and regularly carried, it was

RESOLVED, the following list of 123 candidates shall be and herewith are elected to Fellowship as of this date, and the succeeding list of 9 candidates shall be and are herewith elected as of March 31, 1940 (Editor's Note—This list was published in the January, 1940, issue of this journal).

Upon motion by Dr. Sydney R. Miller, seconded by Dr. Robert A. Cooke, and regularly carried, it was

RESOLVED, the following list of 149 candidates for Associateship shall be and herewith are elected (Editor's Note—This list was published in the January, 1940, issue of this journal).

On recommendation of the Committee on Credentials, the following resolution made by Chairman Miller and seconded by Dr. Walter Palmer was unanimously adopted:

RESOLVED, that Dr. Howard M. Jamieson, Salisbury, Southern Rhodesia, shall be reinstated as a Fellow of this College.

On recommendation of the Committee on Credentials, moved by Chairman Miller, seconded by Dr. George Morris Piersol, and regularly carried, a resolution was adopted dropping seven Associates from the Roster because of failure to qualify for Fellowship within the five-year maximum term, as provided by the By-Laws. Chairman Miller reported that of 92 Associates elected at the December, 1934, meeting of the Board of Regents, 83 had qualified for advancement to Fellowship, 7 had made no effort to qualify and consequently were dropped, and 2 were deceased.

Chairman Miller then referred to a previous resolution of the Board of Regents, directing the Committee on Credentials and the Executive Secretary to formulate revisions of the booklet concerning membership requirements and other salient matters. He said that it was the intention of the Committee to improve the appearance of the booklet so that it shall be in keeping with the proper dignity and the contents should be changed in both form and substance. The substance of the booklet is now divided into four parts: an announcement which simply tells of the College and some of its activities, but not by any means all in its present form; a section which quotes the objects of the College from the Constitution; a section devoted to the discussion of the various types of memberships and the requirements for admission; a section given over to the matter of dues, fees and initiation.

Dr. Miller said the revision of this booklet involves not merely a rewriting to give the announcement a more comprehensive meaning, but it also involves the possibility of making amendments to the By-Laws to incorporate certain requirements which the Committee on Credentials feels should be taken up. Chief among such matters was the action the Regents might take in regard to the requirement that Associates shall be certified by the American Board of Internal Medicine, or the certifying board in an allied specialty, before coming up for Fellowship, on or after some given date yet to be determined. Dr. Miller stated that after consulting members of the Committee on Credentials, he felt that the introductory statement might be used almost in its entirety as it now appears in the College Directory. The use of this statement in appropriate form would obviate the necessity of a separate division devoted to the objects of the College.

At this point, Chairman Miller presented the following summarized statement of the problems which confront the Committee in connection with the revision of the booklet. (See next succeeding three pages.)

Chairman Miller pointed out that any amendments to the By-Laws must be published to the members one month prior to the annual meeting of the College before such amendments can be regularly adopted. Chairman Miller further stated that before the informative booklet is revised definite action should be taken with regard to two specific matters: (1) certification as a prerequisite for Fellowship; (2) the matter of the initiation fee, if such certification is made a prerequisite. The latter, Dr. Miller pointed out, if the College shall make certification a prerequisite for Fellowship, and since the certifying fee required by these boards is $50.00, some consideration should be granted physicians toward a reduction of the initiation fee in the College. Dr. Miller suggested that the Fellowship initiation fee might be adjusted downward, as might also the fee for certification, so that the total fee shall not be greater than the present Fellowship initiation fee.

President Pepper requested Secretary Loveland to review from the Minutes the discussion in the Board of Regents at its last meeting in New Orleans concerning the

proposal of the Credentials Committee regarding certification, whereupon Mr. Loveland stated that Chairman Sydney R. Miller and Dr. George Morris Piersol, a member of the Credentials Committee, proposed that the Board of Regents should establish the regulation that after a certain date all candidates subsequently elected to Associateship should be required to be certified by the American Board of Internal Medicine, or the certifying board in an allied specialty, as a prerequisite for advancement to Fellowship, this requirement, however, not to affect other requirements already specified in the Constitution and By-Laws. It had been suggested, however, that this new requirement might be accepted in lieu of the presentation of case histories and autopsies.

Mr. Loveland stated that it was the opinion of the Credentials Committee that the present By-Laws would not need to be amended, since Article IV, Section a, of the Constitution provides, "Fellows . . . shall have been elected in accordance with the By-Laws and SUCH ADDITIONAL RULES AS THE BOARD OF REGENTS MAY FROM TIME TO TIME ADOPT."

After general discussion by President Pepper and members of the Board of Regents, on motion by Dr. Piersol, seconded by Dr. D. Sclater Lewis, and unanimously adopted, it was

RESOLVED, that on and after April 6, 1940, certification by the American Board of Internal Medicine, or by the appropriate board in their particular specialty, or country, shall be a prerequisite for Fellowship in the College. This rule shall not apply to Associates who shall have been elected prior to that date. (See a succeeding page for the final and approved wording of this regulation.)

Chairman Miller pointed out that the Committee will be confronted from time to time with proposals for election directly to Fellowship, and that the present By-Laws provide that such candidates shall have exceptional qualifications before the Committee may recommend their election. He stated that one of the criticisms of the present informative booklet is that there should be some statement or analysis of what those special qualifications must be. In the discussion that followed, it was apparent that this new regulation shall not necessarily prevent the election of very outstanding candidates directly to Fellowship.

It was suggested by Dr. Cooke that the "special qualifications" for election directly to Fellowship should be more specifically stated. Dr. Sydney R. Miller, Dr. George Morris Piersol and Dr. D. Sclater Lewis were appointed a committee to withdraw from the meeting and to more specifically draw up the exact wording of the resolution, to be submitted in connection with the report of the Committee on Survey and Future Policy, Dr. James Alex. Miller, Chairman.

On motion seconded and regularly carried, the report of the Committee on Credentials was accepted as a whole.

President Pepper called upon Dr. Hugh J. Morgan, Chairman, to present the report of the Committee on Postgraduate Education.

Dr. Morgan reported a meeting of his Committee on December 16, at which a tentative program, as follows, had been drawn up for the series of postgraduate courses to be given during the week or weeks immediately preceding the next Annual Session in Cleveland, April 1–5, 1940:

No. 1. GENERAL MEDICINE—University of Michigan, Dr. Cyrus C. Sturgis, Director.
No. 2. MEDICINE IN INDUSTRY—Henry Ford Hospital, Dr. Frank J. Sladen, Director.
No. 3. HEMATOLOGY—Ohio State University, Dr. Charles A. Doan, Director.
No. 4. METABOLIC DISEASES—Mayo Foundation, Dr. Russell Wilder, Director.

No. 5. Gastrointestinal Diseases—Mayo Foundation, Dr. W. C. Alvarez, Director.

No. 6. Allergy—Roosevelt Hospital, New York City, Dr. Robert A. Cooke, Director.

No. 7. Cardiovascular Diseases—State University of Iowa, Dr. Fred M. Smith, Director.

(Following the meeting of the Board of Regents, it was determined that the two courses at the Mayo Clinic could not be arranged, and they were withdrawn from the schedule.)

Dr. Morgan reported that the Committee had been slow this year in making definite plans relative to the postgraduate courses, because at the last annual meeting, the whole problem of the postgraduate courses, including the content and the conduct, had been considered by the Board of Governors, who had made a survey, and on whose report the Regents' Committee had waited.

Dr. Morgan also reported the request of a private clinic for the College to approve its postgraduate course in psychiatry. The College Committee on Postgraduate Education felt this would be a deviation from its previous duties and questioned the advisability of the College putting its stamp of approval on courses given under private auspices. Without special action, it was apparent that the Regents concurred in this opinion.

Dr. Morgan continued: "The final matter under consideration by the Committee concerns the rôle the College shall play in the field of postgraduate training in institutional practice. I think it would be useful to some members if we review briefly the things that led up to our present position relative to the decision we have made. In 1937, the Committee on Postgraduate Education was informed that the activities of the College in the field of postgraduate training at that time could be publicized at the Annual Meeting and in the 'Annals of Internal Medicine,' and the Board went on record that it wanted to do more than that in the field of postgraduate training, and that we should go into some sort of activity that would exert an influence on the quality of postgraduate training in medicine. At that time we considered an invitation from the American College of Surgeons to join with it in making a survey of hospitals as appropriate places for postgraduate courses in medicine. The Board of Regents and the Committee attended the College of Surgeons' meeting in New York City and received the invitation to go into the surveying of hospitals as places for postgraduate training in medicine. We felt loath to accept immediately, but very seriously considered their invitation. Directly after, the Council on Medical Education and Hospitals of the American Medical Association voiced an interest in this field, and Dr. Cutter, its Secretary, met with the Regents of this College in New Orleans and unofficially invited the College to consider working out some plan of using that Council as a means for making its contribution in this field. Then followed a meeting of the Board of Regents of the College with the Trustees of the American Medical Association in Chicago, the sense of which was that the College and the Council were interested in the same things, and there seemed to be no very good reason why some plan could not be worked out that, provided certain difficulties were ironed out, would enable the College to associate itself in some way with the Council, which was already in the field and doing an expensive piece of work. Representatives from the Board of Regents were then instructed to meet, with Dr. Capps and myself, with the Council on Medical Education and Hospitals at the St. Louis meeting of the American Medical Association, which we did. The Council was there informed of our invitation from the College of Surgeons, and also the Council was informed of those points that led to a feeling of hesitancy relative to our working out a plan with the Council on Medical Education and Hospitals. Two points came out that seemed important: first, the American Medical Association had put itself in a position of

rather decrying the importance of and, perhaps to some extent, of suppressing the expressions of specialty groups in medicine, specialty societies of which we are a very important one; and, second, the Council was brought into being by individual appointments each year of new members. This conference with the Council was very satisfactory, and out of it came an agreement that there certainly should be some plan by which the Council and the College could do a better job in this matter of postgraduate training, insofar as determining criteria for good positions in hospitals, residency training, fellowships, and actually surveying hospitals on the basis of these requirements and criteria.

"An individual from the Council, one from the Postgraduate Committee from the College and one from the American Board of Internal Medicine were appointed to consider some sort of plan whereby the College and the American Board could participate in a significant way with the work that the Council is doing. Your Committee has gone over this plan, which has been evolved, and a copy of which is placed in your hands. (See copy at end of Dr. Morgan's report.)

"The Committee believes that this plan offers a mechanism by which the College can play a very influential rôle in the activities of the Council on Medical Education and Hospitals of the American Medical Association. The Committee believes that one of the most important objections to the establishment of a relationship between the College and the Council was removed at the last meeting of the American Medical Association, in that the election of the Council members was removed from the field of political patronage and is now by election by the House of Delegates on nomination by the Board of Trustees of the American Medical Association. The Committee believes that the American Medical Association has reoriented itself to the governing bodies, certainly in one sense with regard to its attitude toward special societies. There is now a much healthier and more natural feeling with regard to those points. This plan will make it possible for the College, through its appointed representatives, and for the American Board to determine what the criteria are that shall be used in certifying positions as suitable for postgraduate training in medicine as would apply to the whole field in which we have been interested. The actual operation, the actual survey of the hospitals and institutions and study of the positions would be done by the machinery that has already been in existence some years in the Council. The standards would be furnished by this conference committee, and the results would be surveyed, approved or disapproved, by this committee before any action is taken, either by the Council, by the American Board, or by the College, to make the Council's findings official."

CHAIRMAN PEPPER: "This is an extremely lucid report, and brings the matter right up to us as to whether we approve."

DR. MORGAN: "If this proposal is adopted by the College, it must also be adopted by the American Board of Internal Medicine and by the Council of the American Medical Association, and when this is done, this conference committee will come into being."

On motion by Dr. Morgan, seconded by Dr. Stroud, and regularly carried, it was

RESOLVED, that the Board of Regents shall adopt the proposal for the establishment of a conference committee, as presented in the foregoing report, and that the President of the College shall appoint two members to this conference committee to represent the College.

"TENTATIVE PROPOSAL FOR ESTABLISHING A CONFERENCE COMMITTEE CONCERNED WITH GRADUATE TRAINING IN THE FIELD OF INTERNAL MEDICINE

"1. It is proposed that there be created a Conference Committee on Graduate Training in Medicine.

"2. The Conference Committee shall consist of two delegates from each of the following organizations: The American College of Physicians, the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the A. M. A.

"3. The function of the Conference Committee on Graduate Training in Medicine shall be:

"*a*) To submit observations and recommendations which may be useful in furthering the purposes of the constituent organizations.

"*b*) To consider those elements which are regarded as essential in the appraisal of residencies, fellowships and systematic graduate courses for which the approval of the constituent organizations may be sought.

"4. Actual visitation of medical schools and hospitals for the purpose of securing information regarding standards and facilities for instruction in internal medicine shall in general be made by the staff of the Council on Medical Education and Hospitals; the Council will, however, welcome the assistance of qualified representatives of the College and the Board when such assistance is available. Information thus obtained shall be made regularly available to the Conference Committee.

"5. Residencies, fellowships or systematic courses in the field of internal medicine will be considered by the Conference Committee before independent action is taken by any one of the constituent organizations.

"While the foregoing memorandum covers the situation as far as the Committee understands the matter delegated to it, it is the feeling of the Committee that it may well be desirable to include members of other medical specialty boards in a conference pertaining to the problems of graduate training."

Dr. Paullin expressed his hearty approval of the proposal, and Dr. Irons, Chairman of the American Board of Internal Medicine, reported that the American Board had already approved of this proposal. He said the effect of this action by the College will have very farreaching results on the whole situation in graduate medical education.

Dr. Bruce commended the Committee and Dr. Morgan particularly on the successful termination of these conferences.

After the adoption of the resolution, President Pepper appointed to the conference committee Dr. Hugh J. Morgan and Dr. James D. Bruce, the latter appointment to be effective until Dr. Bruce's induction to the Presidency, when he may appoint a successor.

Dr. Hugh J. Morgan pointed out that he had first had the distinct impression that the College, in 1937, wanted to make a conspicuous contribution to the field of postgraduate training, and that the College anticipated the expenditure of funds to carry out such a program. The present plan now adopted, Dr. Morgan said, would not be a conspicuous contribution on the part of the College, but it should be very effective and would cost the College practically nothing.

Dr. Ernest E. Irons, Chairman of the American Board of Internal Medicine, reported that 2,133 physicians had been certified, of which 358 were certified by examination. The Board estimates that the probable number of examinees, 1939–40, will be between 225 and 235; 112 candidates appeared at the October 3, 1939, examination. The Board has labored to improve the quality and dignity of the examinations, and plans to obtain coöperation in examinations with the specialists in cardiology, gastro-enterology, etc. The annual budget of the Board is approximately $5,000.00, and the Board has a balance of $15,000.00. The Board further has approved unanimously the report of the joint committee proposed to establish a conference committee concerned with graduate training in the field of Internal Medicine.

Through questions put by Dr. Cocke and Dr. Paullin, Dr. Irons revealed that the number of failures had been much greater in the early operation of the Board than at present, but that the percentage still is about 23 per cent. For the last examination, the percentage of failures was estimated at about 30 per cent. This was due, Dr. Irons thought, to the fact that the Board has consistently increased the severity of the examination, and due to the fact that many candidates overestimated their degree of preparation. The Board feels that it must maintain its standards, and feels no apprehension about the number of candidates who will present themselves during the next year. The greatest mortality in the examinations naturally had been on the written part, because candidates must pass the written examination before coming up for the oral, and in that manner a larger proportion of the ill-qualified candidates are eliminated.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, told of the progress of former fellowship recipients; specifically, Drs. John Russell Smith, Harold Magnuson and Robert Williams.

The Committee recommended that the fellowship award made to Dr. Kenneth Evelyn, who could not take up the appointment July 1, 1939, be carried over, or re-awarded, for work in physics in medical problems at the Royal Victoria Hospital, Montreal, under the general direction of Dr. Jonathan C. Meakins.

On motion by Dr. Barr, seconded by Dr. Stroud, and unanimously carried, it was

RESOLVED, that the Research Fellowship in the amount of $1,800.00 awarded to Dr. Kenneth Evelyn be re-awarded as of July 1, 1940.

On motion by Dr. Barr, in accordance with recommendations of the Committee on Awards, seconded by Dr. Bruce, and unanimously carried, it was

RESOLVED, that Research Fellowships in the amount of $1,800.00 each be awarded to Dr. Richard Hugh Lyons and Dr. Lewis Dexter, beginning July 1, 1940.

Dr. Barr expressed the regret of the Committee that two additional fellowships were not available to two other promising candidates who had been under consideration.

There followed a general discussion concerning the great value of these fellowships awarded by the College.

On motion by Dr. Hugh J. Morgan, seconded by Dr. Paullin, and regularly carried, it was

RESOLVED, that the Committee on Fellowships and Awards shall select one of the candidates under consideration to whom an additional fellowship was not available as a substitute in case one of those appointed should not be able to accept, or in case an additional fellowship should become available.

Dr. Barr continued his report by stating that the Committee on Fellowships and Awards recommended the award of the John Phillips Memorial Medal for 1940 to Dr. René Dubos. The Committee had sixty representative scientists under consideration.

On motion by Dr. Barr, seconded by Dr. Palmer, and regularly carried, it was

RESOLVED, that the John Phillips Memorial Award for 1940 be made to Dr. René Dubos, of the Rockefeller Institute for Medical Research for fundamental investigations concerning the form, structure and function of microbial cells and concerning the lysis of bacteria; specifically for his studies of lysozyme, an enzyme which lyzes many saprophytic organisms, and for the isolation of a soil bacillus elaborating a substance lethal to pneumococci and other gram positive members of the bacterial species. The award is made with the belief that aside from any or no immediate practical use the investigations have established a new principle of great importance in the study of cellular chemistry and of chemotherapeutic substances.

Dr. James Alex. Miller, Chairman of the Committee on Survey and Future Policy, presented the following report:

"A meeting of the Special Committee on Survey and Future Policy of the American College of Physicians was held at the College Headquarters, Philadelphia, Pa, on December 16, 1939, with the following present:

Dr. James Alex. Miller, *Chairman*
Dr. Jonathan C. Meakins
Dr. Sydney R. Miller
Dr. George Morris Piersol
Dr. Maurice C. Pincoffs

Ex Officio

Dr. O. H. Perry Pepper

"The Chairman of the Committee first outlined the purposes of the Committee as stated in the resolution of the Board of Regents authorizing its appointment. Then, as being also Chairman of the Finance Committee, the Chairman gave a brief review of the financial situation of the College, showing that on December 31, 1935, the cash and security assets of the College were approximately $155,000.00, and that by December 31, 1936, after the present Headquarters were bought, altered and furnished, at an expense of approximately $64,000.00, there remained assets of $115,-500.00. Each year since that time, there has been a surplus of income over expenses of somewhat over $25,000.00 a year, and at the present time the total assets of the College, including the market value of investments and cash in hand, is slightly in excess of $190,000.00. He also stated that the main sources of the surplus were from the initiation fees of new Fellows and the annual profit on the Commercial Exhibits at each Annual Session.

"*Certification and Qualification for Advancement from Associateship to Fellowship:* This question was fully discussed from various angles, and it was the general consensus of opinion that at the proper time, certification from the American Board of Internal Medicine should be a required qualification for advancement to Fellowship, and that this probably might become effective within a comparatively short time, possibly 1941 or 1942. This whole problem is being studied by the Committee on Credentials, of which Dr. Sydney R. Miller is Chairman, and he was requested to keep this Committee informed of the progress of their deliberations and of their proposed recommendations.

"*Initiation Fees and Annual Dues:* There was a thorough discussion of what needs there might be for excessive funds, such as are now being accumulated by the College. Also as to what might be considered the logical objective in the matter of invested endowment for the College. There was no definite action taken, but it appeared to be the general opinion that a gradual increase of capital up to $500,000.00, which would assure a fixed income of approximately $20,000.00 a year, would not be considered excessive. Inasmuch as the program for the increased expenditures for various possibilities has not yet been adopted, it was the general consensus of opinion that at the present time no changes, either in initiation fees or dues, would be wise, but it was brought out in discussion that if the requirement of certification was carried out, the fee for certification examinations, plus the initiation fee, might very well be excessive. In that connection, Dr. J. C. Meakins stated that a surplus was being accumulated in the hands of the American Board of Internal Medicine, and it was their hope that they might gradually diminish the fees for examination. After discussion, it appeared to be the general consensus of opinion of this Committee that a proper adjustment should be made at a suitable time between the fees required for the examination of the American Board of Internal Medicine and initiation fees of the

College, so that possibly the combined fee would not be greater than the present College initiation fee of $80.00.

"*Commercial Exhibits:* Dr. George Morris Piersol, as Chairman of the Commercial Exhibits Committee, reported that the opinion of his Committee was that as present managed and supervised, the Commercial Exhibits had a very considerable educational value, that it was ethically of a high standard and that it would be entirely improper to abolish or curtail these exhibits, as has been at times suggested. The entire Committee agreed with Dr. Piersol that the Commercial exhibits should be continued as at present, with a continuation of the very close supervision and the maintenance of high standards.

Scientific Exhibits: A discussion ensued concerning the suggestion, which at times has been made for the College to institute a Scientific Exhibit in addition to the usual Commercial Exhibit. That there should be a scientific exhibit, it seemed to all of the Committee would be desirable. It was suggested that it might very well begin in a small way, confined to possibly one subject in Internal Medicine for the first year, and that the subject for the exhibit might very well also be made a subject for a symposium of a few papers on the general program. It was brought out that there are a great many scientific exhibits now being conducted, and that it would be very desirable to make a study of their experience. The Committee voted to recommend to the Board of Regents that the present President be authorized to appoint a special committee to investigate the subject of scientific exhibits and report to this Committee on Survey the results of such study.

"*Postgraduate Education:* A general discussion occurred concerning the future possibilities for the College in the line of Postgraduate Education. The experience of the present courses which are given before each Annual Session was discussed, and Dr. O. H. Perry Pepper suggested that the College might very well subsidize these courses in addition to the fees which are now being paid by the students.

Inasmuch as this whole question of Postgraduate Education is being studied by a special Committee of which Dr. Hugh J. Morgan is Chairman, it was suggested that this Committee take no action in this field, but request that it be kept informed of the progress of the studies of Dr. Morgan's committee, and of any recommendations which they may be prepared to make to the Board of Regents. The Committee suggests the possibility of having the Chairman of the Committee on Postgraduate Education made a member ex officio of the Committee on Survey and Future Policy.

"*Fellowships:* The possibility of using funds of the College for additional fellowships was also discussed, and it was voted to request from Dr. Barr that his Committee on Fellowships make recommendations to this Committee of any changes or additions that that Committee may consider desirable.

"*Educational Motion Pictures:* The possibility of the College taking the lead in making educational motion pictures in the field of Internal Medicine available to various teaching institutions was discussed. It was thought desirable that information be collected as to just what pictures of this sort were now available in various parts of the country. Consequently, Dr. M. C. Pincoffs, as Editor of the 'Annals of Internal Medicine,' was requested to put a news note in the 'Annals,' suggesting that the College was interested in having information concerning any such films that are available and asking any one who either possessed such films or had knowledge of where they might exist be requested to communicate such information to President Pepper, in the care of the College.

"*Bulletins Concerning Courses in Internal Medicine:* Dr. M. C. Pincoffs suggested that there was a lack of available information concerning postgraduate courses in Internal Medicine which are available in various parts of the country. It was suggested that the 'Annals' might act as a clearing house for such information by publishing each month a list of such courses with details concerning them. It was

voted by the Committee that Dr. Pincoffs explore these possibilities further and report to the Committee.

"*Development of State and Regional Meetings:* The Committee considered that the development of these local meetings is a very important and logical one for the College, and inasmuch as this program is one especially in the province of the Board of Governors, the Chairman of this Committee was requested to write to the Chairman of the Board of Governors, requesting that this Committee on Survey be informed of the progress that has been made to date and the plans which the Board of Governors have for the future in regard to such local meetings.

Adjournment.

JAMES ALEX. MILLER, *Chairman*
JONATHAN C. MEAKINS,
SYDNEY R. MILLER,
GEORGE MORRIS PIERSOL,
MAURICE C. PINCOFFS,
Ex-Officio
O. H. PERRY PEPPER
Special Committee on Survey and Future Policy"

President Pepper opened the report for general discussion from the floor.

On motion by Dr. Cocke, seconded by several, and regularly carried, it was

RESOLVED, that the President of the College shall appoint a special committee to investigate the subject of scientific exhibits, and to submit a report to the Committee on Survey the results obtained from such study.

President Pepper pointed out that this does not commit the College to a Scientific Exhibit, but merely is a preparation of data for later guidance. President Pepper appointed a Committee to consist of:

Dr. Francis G. Blake, *Chairman*
Dr. Robert A. Cooke
Dr. D. Sclater Lewis

On motion by Dr. Piersol, seconded by Dr. Paullin, and regularly carried, it was

RESOLVED, that the Chairman of the Committee on Postgraduate Education and the Chairman of the Board of Governors shall be added as members of the Committee on Survey and Future Policy.

On motion by Dr. Cocke, seconded by Dr. Palmer, and regularly carried, the report of the Committee on Survey and Future Policy was accepted as a whole.

At this point, the Chairman called upon Dr. Sydney R. Miller, Chairman of the Committee on Credentials, to present the formal motion regarding certification as a prerequisite for advancement to Fellowship. The following resolution was made by Dr. Miller, seconded by Dr. Paullin:

"RESOLVED, that after April 6, 1940, all candidates for Fellowship must present satisfactory evidence of certification by their national board for certification in their particular field, where such a board exists; this rule shall not apply to candidates from the Army, Navy and Public Health Services; it shall not apply to those who have been elected Associates prior to the above date; it may be waived in the cases of those proposed directly for Fellowship because of exceptional and outstanding qualifications."

In the discussion of the motion, Dr. Pincoffs expressed the opinion that this requirement would not seriously affect the number of candidates for Associateship, because it actually will not affect any newly elected Associates until those presented at the autumn, 1940, meeting of the Board of Regents, and these men would not be eligible for consideration for Fellowship for three years, and many would not qualify

until five years, or until 1945. During the interim, the American Board of Internal Medicine will have gained much more momentum, and the number of diplomates will be consequently increasing. Dr. Pincoffs expressed approval of a plan to adjust the Fellowship initiation fee at that time, so that there would be no increased financial burden exacted of this group of Associates because of having to be certified first by the American Board.

Dr. Piersol discussed several aspects of the motion, including:

(1) The American Board of Internal Medicine is now certifying approximately 200 men a year, and that is about the number of Fellows ordinarily elected to the College, which would indicate that there will be an adequate number of certified men available for College membership.

(2) The most important aspect of the proposal for certification affects the Credentials Committee; the Credentials Committee has experienced great difficulty in determining the professional and intellectual qualifications of candidates for Fellowship; the criteria set up in the By-Laws are totally inadequate; the case history system is unsatisfactory; from the earliest time, the Credentials Committee has looked forward to the time when some concrete method of determining the professional eligibility of Fellows could be established, even looking forward to the establishment of examinations by the College; when these certifying boards were established, there was no need to duplicate a complicated machinery; these boards, one of which was established under the College auspices, should be utilized for the technical examinations; the Credentials Committee is at a loss to know of any better method for determining the intellectual ability for Fellowship than this method of examination; if the proposal is adopted, all unnecessary, unreliable and variable means of determining men's ability will be eliminated, and there will be a yardstick which is clear-cut by which the Credentials Committee can definitely measure candidates' abilities.

(3) The adoption of the proposal is not a complicated thing to achieve; the By-Laws and Constitution make it perfectly evident that the Board of Regents may, from time to time, at its discretion, change and set up whatever qualifications they deem wise for Fellowship; no revision of the By-Laws or of the Constitution is necessary.

(4) When the present By-Laws were adopted, this particular provision was added for this specific purpose, so that there would be flexibility in extending the requirements for membership and the methods of applying such requirements.

Dr. Stone prophesied that the adoption of this regulation would not affect the College income from initiation fees more than one-third.

Dr. Fitz, speaking to the motion, said in part, "I am afraid that if we immediately adopt a resolution of this type, we may perhaps be doing something to destroy the present usefulness, ideals and philosophy of the College, because I do not think we have yet proved whether the specialty boards are of permanent value. I am impressed that the men now qualified do so for a variety of reasons. Some men may want to be certified for the sake of advertisement; some think that they can only get hospital positions by being certified, and some think that the scheme is new and fashionable, and are anxious to try it out. I don't think that a board operating so short a time is going to be permanently popular, or really going to be the type of thing that may even be desirable as time goes on. If you assume that more men are going to come up who want to go into general practice, and who do not want to be certified by a board, such as we have, how are you going to take care of them?"

Dr. Pincoffs: "We are to a certain extent committed to a very thorough trial at least, and a very whole-hearted trial, of the assistance of the American Board of

Internal Medicine, which we largely initiated. If this is a critical time in its development, it will be all the more critical if the body that started it is half-hearted in supporting it. This is the time when we should show our full support of the Board and see that it gets a very fair and full trial. Of course, its advantage is that it does attract a great many men for a variety of reasons, some very laudable and some very weak perhaps, but, nevertheless, it makes men work and study, and thereby raises the level of the practice of Internal Medicine."

DR. BRADLEY: "There is another consideration—as long as this proposal will not be written into the Constitution and By-Laws but be adopted merely as another rule of the Regents for the acceptance of Fellows, after trying it for five or six years, we may, without difficulty or delay, change the requirements and substitute others. This is not a regulation that must be made absolute for the future. The Committee on Credentials feels that we have long been postponing the adoption of this rule, but there has now come the time when something must be done, and I think if we are ever going to support the American Board of Internal Medicine we ought to do it now. I am in favor of this motion, and I think the proponents were right in leaving the way open to elect men directly to Fellowship who perhaps for adequate reasons may not be certified."

DR. COCKE: "For the sake of those who are not familiar with the discussions, this proposal does not mean, by any means, that certification is going to admit a man automatically to Fellowship. There will be other conditions and circumstances that the Credentials Committee will investigate before a man will be accepted. That should be specifically stated in the booklet concerning requirements."

President Pepper pointed out that this rule would not become effective until after the Credentials Committee had already passed upon candidates preceding their election to Associateship.

The motion was put and unanimously carried.

Next taken under advisement was the matter of whether or not there should be any amendment to the Constitution or to the By-Laws, because of this newly adopted regulation. Secretary Loveland was asked to read Article IV, paragraph 2, of the Constitution. It was the consensus of opinion that no amendments would be necessary, but that proper announcements should be made.

President Pepper suggested to the Chairman of the Committee on Credentials that that Committee should revise entirely its system of action and prepare a new publication of requirements later on, authorization already having been issued by the Board of Regents for the revision.

Dr. William Gerry Morgan, College Historian, was called upon for a report of progress on the preparation of the History of the College for its quarter of a century. Dr. Morgan stated that the history had been divided into two parts: first, a narrative of the founding and development of the College, and, second, the chronology of the College. The outstanding activities of the College would be presented in such a way that they would stand the test of criticism and of time, and to that end the Historian had invited men to write about certain specific activities of the College, and those men had been chosen because they were all Fellows of the College who had been either sponsors of or highly influential in developing those activities. Dr. George Morris Piersol, as Secretary-General, had contributed the preface for the volume; Dr. Maurice C. Pincoffs, as Editor, had contributed the chapter dealing with the publications of the College; Dr. Walter L. Bierring, as former Chairman of the American Board of Internal Medicine, had contributed the chapter on the part played by the College in the founding of that Board; Mr. E. R. Loveland, as Executive Secretary, had prepared the chapter both on the finances of the College and the development of the Constitution and By-Laws; Dr. Charles F. Martin had contributed a chapter

regarding the reorganization of the College between 1926 and 1929, and Dr. James Alex. Miller had contributed a chapter dealing specifically with the developments of the College from 1928 until 1940, with some prophesy with regard to the future. In the concluding part of the first section of the History, the Historian will have a chapter on the contributions of the Presidents, with a section also devoted to the men in less conspicuous positions who have contributed quite as much in their way to the progress and development of the College. The last section of the History will be called the chronology, and will contain a brief resume of the Minutes of the College which have been available from the beginning of the College in 1915 to the Cleveland meeting in 1940. Dr. Morgan said that the chronology will be of some value, particularly for reference. He estimated that the volume will contain between 300 and 350 pages. There will be approximately 50 illustrations, such as facsimiles of the original charter, various headquarters the College has occupied, its documents, such as the Fellowship Pledge, etc., etc.

Dr. Morgan described the many difficulties experienced in obtaining some of the data and in preparing a factual and interesting account. Dr. Morgan expressed the wish that the present Board of Regents would see fit to authorize the publication of the volume, and to make proper budget provision and to determine the method of distribution.

After general discussion, on motion by Dr. Piersol, seconded by several, it was

RESOLVED, that the Board of Regents authorize the publication of this History in book form and make an appropriation not to exceed $3,000.00 to defray the expenses.

In general discussion that followed, Dr. Pincoffs pointed out that this book would appear in 1940 as an anniversary volume, and suggested that its publication need not be rushed for completion by the Cleveland Session in April, 1940.

There was general discussion as to the type of format, whether it should be distributed to all Fellows and Associates, and other relevant considerations. Secretary Loveland stated that Dr. Morgan had been modest in his presentation, and that Dr. Morgan had been put to some personal expense already in the preparation of the manuscript and for consulting fees with an expert bookmaker regarding a suggested format, type, size of illustrations and other matters. Mr. Loveland suggested that approximately 3,500 copies be published, and that a copy be given without charge to every active Fellow of the College and to new members as they qualified for Fellowship.

Dr. Cocke suggested that Dr. Morgan be reimbursed for all personal expenses he had borne, but Dr. Morgan refused reimbursement, saying that this work had been one of great interest to him, and that his contribution is only a small part of his devotion to the College over a great many years.

Dr. Fitz suggested that extra copies be printed, so that those who wanted to purchase them, either personally or for libraries, would be able to do so.

Mr. Loveland pointed out that the printer could be instructed to hold the type, so that a second printing could be made in case of need. The matters of format and arrangement were left in the hands of the Historian.

On motion by Dr. Blake, seconded by Dr. Bradley, and regularly carried, it was

RESOLVED, that the History shall be distributed to all Masters and Fellows of the College free of charge, regardless of whether the Fellows are paying dues or not.

It was pointed out that the volume will be placed on sale, and the price will be determined by the cost of publication.

Dr. Walter W. Palmer, Chairman of the Committee on the "Annals of Internal Medicine," stated that a meeting had been held to consider a problem brought up by the Editor, namely, the plan of accepting orders and distributing reprints to commer-

cial firms. The Committee, on the Editor's recommendation, suggested that authors shall continue to receive their reprints in any quantities at the published rates, and that they may pass on reprints to commercial firms, subject to the approval of the firms on the part of the Editor.

The Executive Secretary, Mr. Loveland, to clarify the situation, pointed out that the present recommendation would make it necessary that the College accept no orders for reprints from commercial houses, and that the College would in no way benefit from such orders. He explained that in the past, he, as the Business Manager of the ANNALS, had accepted an occasional order for reprints from commercial firms, the orders being approved by the authors, and the reprints furnished on order to the printers from the College. Inasmuch as the College placed the orders with the printers and thus controlled all such commercial orders and at the same time became guarantor for their payment, the commercial concerns were charged a slight mark-up over the prices of reprints to authors. The practice had been followed in accordance with the similar practice of many other scientific societies, and also from the standpoint of an equity on the part of the College to receive some return for its services and for its large investment in the publication of the ANNALS OF INTERNAL MEDICINE. The only particular exception to this practice that he had discovered was that of the American Medical Association, which furnishes reprints to commercial houses at the same rate it furnishes reprints to its authors. However, the American Medical Association is its own publisher and printer, and probably makes a profit not only on the reprints furnished commercial houses, but also on reprints furnished to authors. The American College of Physicians makes not one cent of profit on any reprints furnished to any author, and has as its object the furnishing of reprints to authors at the lowest possible cost. Mr. Loveland pointed out that the College has spent thousands of dollars in establishing its journal, and for the first several years of its publication, the College made up deficits amounting to additional thousands of dollars. Any surplus the College has enjoyed in recent years has not yet been adequate to make up the deficits sustained in the founding of the journal at its beginning. Mr. Loveland further emphasized the importance of controlling the acceptance of orders from commercial houses for reprints, and not to make it possible for the printers to accept such orders without the official sanction and knowledge of the College.

Dr. Pincoffs said that the College should continue its safeguards against the use of Annals articles as advertising matter by commercial firms. At present in those special instances in which there seems to be less objection to such use of reprints and when the author distinctly authorizes such use of his article, orders for reprints are to be handled in such a way that the author take written responsibility for any criticism that may arise in connection therewith. The College should not be further implicated by selling reprints to commercial firms.

Chairman Pepper stated that no action was called for, and the Committee's report would be received.

Dr. Pincoffs had no further report for the "Annals of Internal Medicine."

Dr. Edward L. Bortz, Chairman of the House Committee, could not be present because of illness, but his report was presented by Dr. William D. Stroud, a member of the Committee.

"REPORT OF THE HOUSE COMMITTEE TO THE BOARD OF REGENTS OF THE AMERICAN COLLEGE OF PHYSICIANS FOR DECEMBER 16, 1939

"(1) The House Committee has had three meetings. The majority of the Committee's time has been taken up in the consideration of various suggestions for a suitable painting, portrait, inscription or emblem for the space above the fireplace in the Board Room.

"Several months ago the Committee decided to ask the Editor of the ANNALS to

publish a statement from the Committee requesting suggestions. But one reply was received by the Chairman of the Committee, that being from Dr. Jones of Louisiana, with the suggestion that a frame be made and hinged in place to hold a mirror. Later if a suitable picture were obtained, the mirror could be replaced.

"In a conference with the well-known architect, Mr. Edwin H. Fetterolf, the Committee requested Mr. Fetterolf to submit a sketch of the College Seal, which could be done in lead and suitably proportioned to fit the available space.

"While the Committee had no instructions regarding the amount of funds available for this work, the Committee suggested to Mr. Fetterolf that the charges for the same should not exceed $500.00. It was further explained to the architect that the final decision concerning the nature of the Plaque and the amount to be expended rested entirely with the Board of Regents. That is where the matter stands at the present time.

"(2) Mr. and Mrs. M. R. Wiley, who live in the College home and receive a salary of $100.00 a month, were engaged by Mr. Loveland as of June 1, 1939, to act as caretakers for the building and property at 4200 Pine Street. They occupy the rooms on the third floor. Their services have been satisfactory.

"(3) The building and property are in excellent condition. The cost of maintenance, including wages of caretakers, light, heat, gas and water, fire and liability insurance, taxes, compensation insurance, and general maintenance, for the year 1939 will be approximately $3,470.00. The cost of rent and maintenance of the old offices at 36th & Walnut Streets, as far back as 1931, amounted to $3,137.00, only a slight amount less for three small offices that were entirely inadequate and unsuited to the purpose. It might be appropriate to add to the present maintenance of the College Headquarters the allowance for depreciation of $1,000.00. According to the directions of the Regents, the building is being depreciated $1,000.00 per annum, until the valuation is reduced to the appraisal value of the land alone.

"During the past year, a guest room on the second floor has been appropriately furnished for the use of Officers, Regents and Committeemen who may come to Philadelphia on College business.

Respectfully submitted,

The House Committee—
T. GRIER MILLER
WILLIAM D. STROUD
EDWARD L. BORTZ, *Chairman*"

In commenting upon the report, Dr. Stroud said that the Committee did not specifically recommend the acceptance of the report, leaving the matter to the discretion of the Board of Regents. The Committee felt, however, the report embodied the best solution of the treatment of the mantel space in the Board Room. The Committee had tried to find a portrait, or get some suggestions for a portrait, or a painting.

A motion made by Dr. Hugh J. Morgan, seconded by Dr. Cocke, providing for the acceptance of the report, was later withdrawn after discussion.

President Pepper said that he had been keenly interested in the Headquarters, and had hoped that an appropriate painting would some time come to our attention. He spoke unfavorably to the proposal to use a colored Seal of the College in the Board Room.

On motion by Dr. Cocke, seconded and regularly carried, it was

RESOLVED, that the House Committee shall continue its study further in an effort to find an appropriate painting for the College Headquarters' Board Room.

Dr. William D. Stroud, as Treasurer, presented the following report, which, on motion made, seconded and carried, was accepted:

"The present holdings of the College amount to $90,403.75 in Bonds and $84,255.00 in Stocks, at the present market price. Of this amount, $70,948.75 in Bonds are in the Endowment Fund; $19,455.00 in Bonds and $84,255.00 in Stocks are in the General Fund. All the securities of the College cost $177,252.56, whereas the present quotations amounted to $174,658.75, showing a depreciation of $2,593.81.

"As of 'March 19, 1939' (as reported at the New Orleans Session), our invested principal in the Endowment Fund was $68,494.98 in Bonds; our General Fund, $34,855.50 in Bonds and $57,390.95 in Stocks, making a total value of $160,751.43. The book value of that date was $161,085.00, or a profit on investments of $333.57."

Dr. James Alex. Miller, Chairman of the Committee on Finance, presented the following report, and filed a copy of the Minutes of the Finance Committee's meeting held December 16, in which specific purchase and sales of securities were authorized.

"The Finance Committee reports to the Board of Regents that the finances of the College are in extraordinarily sound condition, as already has been reported by the Treasurer.

"Quite a number of sales and purchases have been made during the year, all of which have been made on the advice of the Girard Trust Company, whose advisory service continues to give great satisfaction. It is to be noted that the present market value of all our securities is approximately $174,000.00, while the purchase value is $177,000.00, a decrease of only $3,000.00, or 98.31 per cent in the value of the principal investment.

"The Finance Committee also recommends to the Board of Regents that securities of approximately $30,000.00 market value be transferred from the General Fund to the Endowment Fund, thus bringing the market value of the Endowment Fund up to approximately $100,000.00.

"It is also recommended that the selection of the particular securities to be so transferred be left with power to the Treasurer, with the advice of the Girard Trust Company.

"The Finance Committee has carefully considered the budget as presented by the Executive Secretary and, as presented, it has been approved with the following exceptions:

(1) That the estimated income from investments be increased from $5,700.00 to $7,000.00, this being justified by the estimate of the Girard Trust Company;
(2) The Finance Committee voted to recommend to the Board of Regents that the budget for the Executive Secretary's Office be increased by $600.00, for increases in compensation to members of the office staff.
(3) It was also recommended that an addition of $200.00 be made to the budget for the President's Office for traveling expenses for the President.

Respectfully submitted,
JAMES ALEX. MILLER, *Chairman*,
CHARLES T. STONE,
WILLIAM D. STROUD,
Committee on Finance"

Dr. Miller presented financial reports showing income and expenses (estimated for December, 1939), budget comparisons with expenditures, cost analyses for the ANNALS OF INTERNAL MEDICINE, comparative cost analyses for the Annual Sessions and budgets estimating income and expenditures for 1940.

On motion by Dr. Hugh J. Morgan, seconded by Dr. Stroud, and regularly carried, it was

RESOLVED, that the Board of Regents approve of the transfer of approximately $30,000.00, market value, of securities from the General Fund to the Endowment

Fund, the selection of the particular securities so transferred being left with power to the Treasurer, with the advice of the Girard Trust Company as Investment Counselor.

Dr. Miller, commenting on his report, said: "It is a disappointment to me as Chairman of the Finance Committee not to be able to recommend that the Committee approve a recommendation for additional fellowships. If that had come before us I am sure the Finance Committee would have approved the additional fellowships after hearing the report this morning of the Fellowship Committee. Perhaps it is not too late.

"I would just like to speak on one or two things. The first thing is to point out the extraordinary successful situation in regard to the "Annals." As you know, the subscriptions and advertising have been definitely increasing. We all know what an extraordinary successful journal it is going to be and now we are making a profit estimated in the neighborhood of $6,000.00. There has been some comment about the very low cost of the College Headquarters. It is still hoped that in some way or other we may become tax exempt. Our taxes are about $1,200.00. Since similar activities do not pay taxes, it would seem that a further effort might be made in that direction, and I think the Finance Committee would approve of suggesting to the Regents, at any rate, that further efforts be made to secure exemption from taxes."

On motion by Dr. Cocke, seconded by Dr. Hugh J. Morgan, and regularly carried, it was

RESOLVED, that $600.00 additional, under item "2" of the Finance Committee's report, be appropriated and added to the 1940 budget.

On motion by Dr. Cocke, seconded by Dr. Hugh J. Morgan, and regularly carried it was

RESOLVED, that $200.00 be added to the President's budget to be drawn upon for traveling expenses.

It was understood that this appropriation should apply also to the budget for 1939, as well as the budget for 1940.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, recommended that inasmuch as the Committee has two men of excellent caliber, who might be encouraged by the College to continue their work, two extra fellowships be awarded this year, beginning July 1, 1940, but in doing so, the College shall not make that a necessary precedent for subsequent years.

Dr. Barr pointed out that the College has been experimenting to some extent with these fellowships, and that it is possible as time goes along, the College may give more fellowships, or may change the character of these grants.

On motion by Dr. Barr, seconded by Dr. Bradley, and regularly carried, it was

RESOLVED, that the Board of Regents award two additional Research Fellowships, starting July 1, 1940, in the amount of $1,800.00 each, to Dr. William Woods Beckman and Dr. Morris Tager.

Dr. Hugh J. Morgan, as Chairman of the Committee on Postgraduate Education, asked for the Regents' reaction to a plan by which the College would recognize the effort that men put into postgraduate teaching in the courses sponsored by the College by granting honoraria, supplementing the registration fees collected by the College. For instance, if the College has a group of ten, twenty or thirty men under the direction of some one person in a clinic or hospital for a week or two, would it not be a matter of good policy for the College to see that the director at least gets a sub-

stantial honorarium to the end that he will devote a substantial part of his time and thought to that work?

On inquiry to Mr. Loveland, it was revealed that the College expended $566.15 during 1938, and $462.27 during 1939 on the Postgraduate Courses, in addition to turning over all registration fees collected.

To be more concrete, Dr. Morgan suggested that the director of a two-weeks' course might be given an additional honorarium of $250.00, and the directors of one-week courses might be given honoraria of $150.00.

Dr. Cocke reported that he had heard criticisms that the heads of departments had not participated in the Postgraduate Courses, or given as liberally of their time as they should, and that Dr. Morgan's suggestion was one to encourage more active participation by such heads in these Courses sponsored by the College.

No action was taken making any appropriation or approving the plan of additional honoraria for directors of courses.

Dr. Meakins, as a guest at the Regents' meeting and a member of the American Board of Internal Medicine, was asked to express his opinions concerning the extension of fellowships. Dr. Meakins pointed out that the supply of assistant residencies and resident positions in teaching hospitals had become in many instances exhausted, and many young men who are aspiring to these positions must get their training in other ways. He suggested that good non-teaching hospitals might be stimulated to open assistant residencies and extend a resident system more completely than at present. He said there is a group of extremely good young men who could be helped by fellowships, but since there is a limit on the number that may be granted, the possibility, feasibility or advisability of creating loan funds at a nominal rate of interest to suitable candidates should be thoroughly investigated.

President Pepper pointed out that the College already has a Committee on Revolving Loan Funds, but that the Committee has not worked out an operating plan for adoption by the Regents.

On recommendation and motion by Dr. James Alex. Miller, seconded by Dr. Cocke, and regularly carried, it was

RESOLVED, that the Board of Regents adopt the 1940 budget, calling for an estimated income of $105,600.00, and estimated expenditures of $80,875.00.

President Pepper reported on arrangements for the Cleveland Session. He had attempted to meet criticisms of previous programs, to increase the number of papers by members of the College and reduce the number of guests, also to eliminate to a degree the repetitions of the same speakers that had appeared on our programs in previous years. By reducing the number of guest speakers the cost for traveling expenses likewise would be reduced. One session had been composed entirely of military papers, with the Surgeon Generals coöperating.

Dr. Pepper stated that he wishes to give a President's dinner to the Regents and selected guests, but would like to change the time of the dinner from Wednesday evening, preceding the Convocation, to another evening that would be free and not subject to the hurry entailed if the dinner were held preceding the Convocation. He reported that Dr. Charles F. Martin, the only Master of the College, had accepted the invitation to give the Convocation address. Dr. Martin is a survivor of a period when many interesting things happened in the reorganization of the College, and he will give a broad talk on the history of the College and its growth.

Dr. Pepper stated that he would like to depart from the usual formal Convocation procedure by personally introducing Dr. Martin in a more personal manner than by having his address announced formally by the Marshal.

Dr. Pepper further said that he had told the General Chairman, Dr. Howard T. Karsner, that it would be unnecessary for him to attend this meeting of the Regents,

and that by personal conversation, every possible point of importance had been covered in the preparations for the Cleveland Session.

Dr. Pepper described the program of local arrangements, appointment of committees by Dr. Karsner, the preparation of the clinic program by Dr. Joseph Hayman, Jr., and the preparation of the panel program by Dr. Harold Feil. Panels have been substituted in the place of the so-called round tables.

Dr. Pepper also spoke about local arrangements for the Smoker, entertainment of visiting women, the banquet, and other social matters. President Pepper had posted the program for the Cleveland Session in the Board Room for examination by all.

The Executive Secretary, Mr. Loveland, reported on business arrangements for the Session, including hotels, the auditorium, technical exhibit, Regents'-Governors' dinner, etc. He asked for directions from the Regents as to whether the dinner shall be a subscription dinner or one paid for by the College, the latter plan having been initiated last year.

President Pepper pointed out that the Regents'-Governors' dinner is conducted for the purpose of informal discussion and promotion of College matters. He expressed the hope that the dinner would be kept on a high plane, and would avoid, on one hand, formal speeches, but, on the other hand, would be open for formal discussion by any one who had ideas to present.

On motion by Dr. Paullin, seconded by Dr. Stroud, and regularly carried, it was

RESOLVED, that the expenses for the Regents'-Governors' Dinner be defrayed by the College.

President Pepper asked for suggestions from the Regents as to subjects that might properly and with benefit be discussed at the dinner, and suggested that the Chairman of the Board of Governors nominate some members from the Board of Governors to open discussion of important problems.

The Executive Secretary, Mr. Loveland, called the attention of the Board to possible meeting places for the College in 1941, pointing out that the city is selected at the last meeting of the Board of Regents during the Annual Session. He suggested that if any Regents have particular invitations in mind they be initiated without delay, so that all could receive proper consideration and investigation before time for voting arrives.

The following announcements were read: the next meetings of the Committee on Credentials are scheduled for February 25, 1940, at the College Headquarters, Philadelphia, and on March 31, 1940, at Cleveland; the next meeting of the Board of Regents will occur at 2:30 p.m., March 31, 1940, at Cleveland.

Adjournment.

Attest: EDWARD R. LOVELAND,
Executive Secretary

DR. JOSIAH NEWHALL HALL

Dr. Josiah Newhall Hall, F.A.C.P., aged 80, of Denver, Colorado, died December 17, 1939, in Denver of pneumonia and myocarditis.

Josiah Newhall Hall, born North Chelsea (now Revere), Massachusetts, October 11, 1859, descended from John Hall, who came from England in 1652 and settled in Medford, Massachusetts. Father, Stephen Augustus Hall, a California "forty-niner," later farmer in Massachusetts. Mother, Evalina Amanda (Newhall) Hall, daughter of General Josiah Newhall of Lynnfield, Massachusetts. Bachelor of Science, Massachusetts Agricultural College, 1878, M.D., Harvard Medical School, 1882. House Physician Boston City Hospital, eighteen months.

Dr. Hall came to Denver, February 14, 1883, and on June 25, 1883, settled at Sterling, Colorado, then the only town (250 inhabitants) in a section of North East Colorado, larger than the State of Massachusetts. Three years later, Dr. Hubert Work, a later President of the A.M.A., Secretary of the Interior and Postmaster General, settled in Ft. Morgan, 45 miles away. These two men were the only physicians in that region. Dr. Hall was Mayor of Sterling in 1888–89. In 1892 he came to Denver. In 1891 he was President of the Colorado State Board of Medical Examiners and in 1903–04, President of the State Board of Health. In 1900 he was President of the Colorado State Medical Society. In 1916–17, he was President of the American Therapeutic Society. Dr. Hall wrote over one hundred and forty articles for the medical press. He also wrote the section on gunshot wounds, burns and scalds for Haines and Peterson's Legal Medicine and Toxicology. He wrote "Borderline Diseases," published by Appleton & Company in 1915. In 1893–97 he was Professor of Therapeutics at the University of Colorado. In 1897–1902 he was Professor of Medicine at the Gross Medical College and later at the Denver and Gross Medical College, which afterwards merged with the University of Colorado School of Medicine. In the last years of his life, he was Professor of Medicine Emeritus at the University of Colorado School of Medicine. In 1921–31 he served on the Judicial Council of the American Medical Association. Quite recently he published for private circulation among the members of the Colorado State Medical Society, his personal reminiscences of a busy, useful and most interesting professional life. The first of January, 1936, he was the earliest physician as to time of registration still active as a member of the State Medical Society.

During the war, he was Major in the Medical Corps and served 21 months, first as Chief of Medical Service at the Base Hospital, Camp Logan, Texas and then as Consultant in internal medicine to the Base Hospitals of the Southwest and Western cantonment base hospitals, and six other hospitals with a total of 30,000 beds. During this service he organized teaching clinics at various hospitals. During his professional career, Dr. Hall cared for several hundred of his colleagues affected with tuberculosis.

On April 12, 1885, Dr. Hall married Carrie G. Ayres, daughter of Felix G. Ayres, planter of Davis Mills, Mississippi. He had two sons, Sigourney D. Hall, automobile dealer at Fort Collins, and Oliver W. Hall, who died in Officers Training Camp, January 13, 1919.

Dr. Hall became a Fellow of the American College of Physicians in 1917, being one of the earliest members from the Rocky Mountain district. He was a member of the Board of Regents of the College and served as Governor for Colorado from 1925 until 1932.

Dr. Hall's interest in the history of the western country where he had made his home was given practical form in 1928 by the establishment of the Mrs. J. N. Hall Foundation for marking historic sites. Through the income from this $5000 endowment, supplemented by additional funds from the same donor, the Colorado State Historical Society has been enabled to mark with bronze plaques more than forty sites of historical interest in Colorado.

Dr. Hall combined an amazingly alert mind with a retentive memory and an abundant energy even up to the last few months of his life. He was noted in the Rocky Mountain district for his brilliant diagnoses. He was greatly admired and revered by all his colleagues and "was widely beloved as a sincere, earnest, capable physician, as a leader in establishing the ethics and the true tradition of medical service."

JAMES J. WARING, M.D., F.A.C.P.,
Governor for Colorado

DR. DAVID MURRAY COWIE

David Murray Cowie, Professor of Pediatrics and Infectious Diseases and Chairman of the Department of Pediatrics at the University of Michigan Medical School, died on January 27, 1940, of coronary thrombosis.

Dr. Cowie was born in Moncton, New Brunswick, Canada, on November 19, 1872, and received his early education there. In 1889 he entered Battle Creek College where he studied for three years before enrolling in the University of Michigan Medical School from which he graduated in 1896. He was appointed assistant to the Professor of Theory and Practice of Medicine, Dr. George Dock, immediately after graduation, thus beginning a long and distinguished career in teaching, research and the practice of medicine. In 1906 he was made Instructor in Pediatrics and in 1907, Clinical Professor of Pediatrics and Internal Medicine. The following year was spent with Professor Krehl in Heidelberg. Upon his return to Michigan he resumed his duties in the Medical School and his private practice, and in 1920 was made Professor of Pediatrics and Infectious Diseases and head of the newly authorized Department. He held this position until his death.

His bibliography of over one hundred papers reveals a wide diversity of clinical and scientific interests. One finds the early years occupied in the analysis of various laboratory procedures and clinical technics of internal

medicine, with many contributions in gastro-enterology. This interest gradually merged into the more general fields of internal medicine and continued with the assumption of his responsibility for the teaching of pediatrics. During the two decades of his incumbency of the chair of pediatrics and infectious diseases, while he devoted himself to teaching, writing and research in that field, he always maintained an active interest in the broad aspects of internal medicine, enjoying in both fields a large, consulting practice.

Dr. Cowie served on the Council of the American Pediatric Society from 1913 to 1920 and was elected president of the Society in 1923. He was a Fellow of the American College of Physicians, the American Academy of Pediatrics, and the American Association for the Advancement of Science. He was president of the Michigan Allergy Society in 1937–38, chairman of the iodized salt committee of the Michigan State Medical Society since 1922, secretary of the University of Michigan Pediatric and Infectious Disease Society since 1933, and vice-president in 1920–21 of the American Society for the Advancement of Clinical Investigation. He was a member of the American Heart Association, International League against Epilepsy, Michigan Academy of Science, the Nova Scotia Historical Society and the Michigan Historical Society.

Dr. Cowie was a rare combination of the ideal family doctor, the wise professor, the able research worker, the skillful specialist, excellent teacher, efficient organizer and executive and, above all, an unselfish, loyal friend.

Thus is ended a distinguished career, marked by enthusiasm, energy, sacrifice, high intelligence and painstaking devotion to teaching, research and the care of the sick. He will be long and gratefully remembered by his colleagues, his students, particularly those whose good fortune it was to work intimately with him, and by a large and loyal group to whom he was always the beloved physician. JAMES D. BRUCE, M.D., F.A.C.P.

DR. FRANK HURD ROBINSON, JR.

The accidental death of Dr. Frank H. Robinson, Jr., of the Rockefeller Institute for Medical Research, New York City, an Associate of the American College of Physicians, in an automobile accident in Jamestown, N. Y., November 22, 1939, just at the time when he had begun to employ his splendidly trained talents in the practice of medicine, was not only a great loss to his community but to scientific medicine. Few physicians have brought to the practical application of medicine so many years of fruitful preparation.

As his teacher and advisor, through his medical studies and postgraduate work, I can affirm that he was the type of student that brings joy to a teacher's heart. Earnest, conscientious and ambitious to contribute to scientific medicine, he never failed to carry to a successful conclusion any problem to which he set himself.

His field work in the epidemiology of brucellosis, which was done in conjunction with the National Government, earned high praise, and his sub-

sequent work at the Rockefeller Hospital served only to confirm the reputation which his earlier work at Duke University had created.

This is not the place to review in detail Frank Robinson's scientific publications; these are recorded in medical literature for all time. One thinks, rather, of Frank Robinson the cheerful friend and happy companion. All who knew him called him "Robbie" and the diminutive was one of affection. He was very serious when at work, but loved to play, and a party was always a jolly one when Robbie was there. He had a sound mind in a sound body and rejoiced in using both in all forms of professional and social activity. His death has left a void in the hearts of his friends who will always remember him with a wistful sadness because of his all too early death.

FREDERIC M. HANES, M.D., F.A.C.P.,
Durham, North Carolina

DR. NORMAN IRVING BROADWATER

Dr. Norman Irving Broadwater (Associate) of Oakland, Md., died January 3, 1940, in the Memorial Hospital at Cumberland, Md., of cerebral hemorrhage.

Dr. Broadwater was born in 1882 and received his medical training at the University of Maryland School of Medicine and College of Physicians and Surgeons, graduating in 1909. He had been an Associate of the American College of Physicians since 1926, having originally been a member of the American Congress on Internal Medicine from 1924.

Dr. Broadwater through his ability as a careful clinician and his kindly interest in his patients occupied an important position in the field of internal medicine in his community. His death is a great loss to his many devoted patients and to his large circle of friends in the medical profession.

DR. PETER CLINTON PUMYEA

Dr. Peter Clinton Pumyea was born in Hightstown, N. J., November 8, 1880 and died January 18, 1940.

Dr. Pumyea received his B.S. degree at Princeton University in 1901 and his degree of Doctor of Medicine at Columbia University College of Physicians and Surgeons in 1905. He served an internship at City Hospital in 1906 and started the practice of medicine in 1907 in New York City. He was formerly Director of the Medical Service and President of Medical Board at The Central Neurological Hospital; Attending Physician at Welfare Hospital; Associate, Cardiac Clinic at Roosevelt Hospital; in 1939 he became a member of the Welfare Hospital for chronic diseases as Visiting Physician in Medicine (open Division). He was a Member of the New York State Medical Society, the New York Academy of Medicine, The American Medical Association, and an Associate of the American College of Physicians since 1916.

CHARLES F. TENNEY, M.D., F.A.C.P.,
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